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(54) **Title:** NUCLEIC ACIDS AND ENCODED POLYPEPTIDES FOR USE IN LIVER DISORDERS AND EPITHELIAL CANCER

(57) **Abstract:** The invention relates to nucleic acids and to corresponding encoded polypeptides and to their use for the diagnosis, prevention and/or treatment of liver disorders and neoplastic disorders, especially cancer of the liver and other epithelial tissues, benign liver neoplasms such as adenoma and other proliferative liver disorders such as focal nodular hyperplasia (FNH) and cirrhosis. The invention further relates to methods of diagnosing and treating these disorders.

Description

NUCLEIC ACIDS AND ENCODED POLYPEPTIDES FOR USE IN LIVER DISORDERS AND EPITHELIAL CANCER.

Technical Field

[001] The invention relates to nucleotides and to corresponding encoded proteins and to their use for the diagnosis, prevention and/or treatment of liver disorders and neoplastic disorders, especially cancer of the liver and other epithelial tissues, benign liver neoplasms such as adenoma and other proliferative liver disorders such as focal nodular hyperplasia (FNH) and cirrhosis. The invention further relates to methods of diagnosing and treating these disorders.

[002] The development of cancer in general is characterized by genetic mutations that alter activity of important cellular pathways including, for example, proliferation, apoptosis (cell death), response to stress and epithelial/stroma interactions. It is increasingly recognized that identification of nucleic acids that are deregulated in cancer can provide important new insight into the mechanisms of neoplastic transformation. Identification of deregulated nucleic acid expression in precancerous stages, such as macro regenerative nodules and the "large" and "small" cell change in liver cancer, provide understanding of early events in malignant transformation. Similarly, identification of deregulated gene expression in disorders characterized by tissue proliferation and remodeling, such as FNH and cirrhosis in the liver may distinguish nucleic acids involved in proliferation and malignant transformation. Together such deregulated nucleic acids and the encoded gene products have potential as new diagnostic markers for cancer. Moreover, the products of these deregulated nucleic acids *per se* are targets for therapeutic intervention in the prevention and/or treatment of these disorders in human patients.

[003] The liver plays a vital role in the metabolism of proteins, lipids, carbohydrates, nucleic acids and vitamins. There are numerous disorders effecting the liver that cannot be diagnosed, prevented or treated effectively, such as hepatocellular carcinoma (HCC). Examination of HCC is particularly well suited for the identification of deregulated gene expression in cancer. This is because tissue samples of HCC can be obtained from surgically resected tumors and the tumors are well circumscribed solid structures with little stromal tissue. Furthermore, as indicated above, there is the possibility for comparative analyses of benign and malignant tumors as well as cirrhosis, a non-neoplastic condition. If the limitations in the art of identifying differentially expressed genes associated with liver disorders could be overcome, this comparative approach may enable identification of deregulated nucleic acids

specifically involved in the processes of cellular proliferation and tissue remodeling in a mature organ (e.g., in cirrhosis) as well as the identification and discrimination of gene expression alterations associated with hyperplasia (such as FNH) and with benign and malignant neoplasms (e.g., adenoma and HCC). In HCC there is an urgent need for new and better diagnostic and therapeutic capabilities. Deregulated genes in liver cancer may also be highly relevant to other cancers of the gastrointestinal tract and indeed with other carcinomas (epithelial derived cancers) as these tissues share a common embryological origin.

[004] On a global basis, hepatocellular carcinoma (HCC) belongs to the most common malignant tumors accounting for about 1 million deaths/year (Ishak et al., 1999, Atlas of Tumor Pathology. Fascicle 31. Armed Forces Institute of Pathology, Washington, DC).

[005] Definitive diagnosis of neoplastic liver disorders such as HCC and many other tumors relies upon histopathological evaluation of biopsy specimens. This invasive surgical procedure is generally not undertaken until symptoms appear and the disease is then most often in advanced stages, thereby limiting therapeutic intervention options. Thus there is a need to improve diagnostics and methods of diagnosis. In addition, early diagnosis is crucial but hampered by late onset or even a lack of specific clinical symptoms. At diagnosis most HCC tumors are no longer amenable to surgical resection (except encapsulated tumors or the fibrolamellar variants) (Chen and Jeng, 1997, J. Gastroenterol. Hepatol.,, 12:329-34); moreover, they are highly resistant to cytostatic therapy (Kawata et al., 2001, Br. J. Cancer, 84:886-91). Overall, death usually occurs within 1 year after diagnosis. Thus, markers for early detection, prognostic indicators, and effective prevention and/or treatment regimens for HCC are highly desirable in this field.

[006] In contrast, unlike the well-studied situation in colorectal cancer, liver adenoma may not represent a precursor lesion of HCC. Similarly, although cirrhosis and hepatitis viral infections are clearly risk factors for HCC, these conditions are not pre-requisite for the development of HCC. Certain liver lesions may represent HCC prestages such as macro regenerative nodular hyperplasia, but this is not yet confirmed (Shortell and Schwartz, 1991, Surg Gynecol Obstet., 173:426-31; Anthony, P. in MacSween et al, eds. Pathology of the Liver. 2001, Churchill Livingstone, Edinburgh). Although these disorders are diagnosed by histopathological investigation of liver resections and liver biopsies, no efficient method exists for earlier or non-invasive detection of these conditions. Again, there is immediate need for diagnostic and prognostic markers for these neoplasms and for non-invasive detection of these disorders.

[007] Within the past decade, several technologies have made it possible to monitor the

expression level of a large number of transcripts within a cell at any one time (see, e.g., Schena et al., 1995, Science, 270:467-470; Blanchard et al., 1996, Nature Biotechnology, 1996, 14:1649). Transcript array technology has been utilized for the identification of genes that are up regulated or down regulated in various disordered states. Several recent studies have utilized this technology to examine changes in gene expression in HCC. These studies have variously revealed deregulation (i.e., over- and underexpression) of genes encoding liver specific proteins in HCC cell lines and HCC tissues relative to controls. Moreover the studies revealed genes essential for cell cycle control, stress response, apoptosis, lipid metabolism, cell-cell-interaction, DNA repair and cytokine and growth factor production (e.g., Graveel et al, 2001, Oncogene, 20:2704-12; Tackels-Horne et al, 2001, Cancer, 92: 395-405; Xu et al, 2001, Cancer Res., 61:3176-81). However, there is little concordance in the gene expression patterns reported in these studies that may be due to differences in experimental design and/or to the heterogeneity of HCC tissue *per se*. Moreover, the etiologies of these HCCs are an important factor. Chronic hepatitis B and C virus infections are the major causes of HCC but damage from alcohol and chronic liver metabolic disorders are also recognized to result in HCC and the mechanisms responsible for development of a tumor from these different etiologies are likely to differ. Taken together, until now no satisfactory diagnostics and methods of diagnosing have been developed in order to be able to intervene in liver disorders.

[008] The same applies to the therapy of liver disorders, and epithelial cancers. For HCC for instance, there is no effective therapeutic option except resection and transplantation but these approaches are only applicable in early stages of HCC, limited by the access to donor livers, and associated with severe risks for the patient. In addition, these approaches are extremely expensive. These cancers respond very poorly to chemotherapeutics, most likely due the normal liver function in detoxification and export of harmful compounds. Several other therapeutic options, such as chemoembolization, cryotherapy and ethanol injection are still in an experimental phase and the efficacy of these is not established. Surgical intervention remains the best treatment option but it is not possible to define with precision the extent of the tumor. This invasive procedure therefore, is suboptimal from the perspective of treatment. Furthermore, the lack of early diagnostics for specific liver dysfunctions leads most often to advanced progression of the disease that further confounds therapeutic options and dramatically increases patient mortality from these diseases (Jansen P.L., 1999, Neth. J. Med., 55:287-292). Thus until now no satisfactory therapies have been developed in order to be able to intervene in liver disorders, and other epithelial cancers. Furthermore, in the state of the art, recognition of the different subtypes of liver disorders such as HCC precursor lesions, benign liver neoplasms, and metabolic

liver diseases such as alcoholic liver disease and cirrhosis, as revealed by differential gene expression, have not been disclosed. A summary of the key disease features of some of the disorders evaluated in the invention is provided in Table 1.

[009] **Table 1: Diseases features**

Table 1

DISORDER	Cellular proliferation	Tissue remodeling	Clonal cell expansion	Neoplasia	Transformation/ Malignant potential
Cirrhosis	+	+			
FNH	+	+	+/-		
Adenoma	+	+	+	+	
HCC	+	+	+	+	+

Summary of the Invention

[010] The invention relates to nucleotides and to corresponding encoded proteins and their use for the diagnosis, prevention and/or treatment of liver disorders, especially of hepatocellular carcinoma (HCC), and epithelial cancers, pre-cancerous liver lesions, benign neoplasms such as adenoma, and other proliferative liver disorders such as focal nodular hyperplasia (FNH) and cirrhosis. The invention also relates to vectors and cells comprising such nucleic acids, and to antibodies or antibody fragments directed against said polypeptides and nucleic acids.

[011] The invention further relates to methods of diagnosing and treating these disorders. The evaluation of multiple disorders with overlapping but distinct morphological and clinical features provides new information for identification and discrimination and ultimately new therapeutic strategies for these disorders according to invention.

Disclosure of Invention

[012] A unique approach employed in this invention utilizes discrete, pathologist-confirmed liver cancer pathologies for production of disease specific cDNA libraries enriched in genes specifically up- and down-regulated in HCC compared with a pool of non-neoplastic human livers. The library is a genome-wide representation of deregulated gene expression in HCC and therefore includes all potential HCC deregulated genes. Repetitive hybridization to these library clones with labeled expressed nucleic acids from many additional discrete, pathologist-confirmed liver cancer samples (HCCs) and non-malignant liver lesions indicated nucleic acids highly deregulated in HCC. The surprising finding is that this approach provides deregulated

nucleic acids that had not previously been identified as well as many deregulated nucleic acids that were not before associated with HCC, the elevated expression of which can also be associated with other neoplasms. These HCC deregulated genes and proteins are the subject of this invention.

[013] The screening and verification strategy is already inventive *per se* owing to the elaborate and defined choice of parameters. Identification of differentially expressed genes according to the invention relies upon histopathologically distinguished liver disease tissue for comparison of gene expression changes in disorders of the human liver. Non-diseased reference liver samples for the experiments are also diagnostically confirmed.

[014] The object of the invention is a method of diagnosis of a liver disorder, liver cancer and/or epithelial cancer, wherein at least one compound selected from the group consisting of a polypeptide according to the sequence SEQ ID 1 to SEQ ID 93 (Table 2A to 2D), a functional variant thereof, a nucleic acid encoding one of the afore-mentioned polypeptides, a variant of one of the aforementioned nucleic acids, an antibody or a fragment of the antibody directed against one of the aforementioned polypeptides, or variants thereof, is identified in the sample of a patient and compared with at least one compound of a reference library or of a reference sample.

[015] Another object of the invention is a method of treating a patient suffering from a liver disorder or an epithelial cancer, wherein at least one compound selected from the group consisting of a polypeptide according to the SEQ ID 1 to SEQ ID 93, a functional variant of one of the aforementioned polypeptides, a nucleic acid encoding one of the aforementioned polypeptides or a functional variant thereof, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the aforementioned vector, an antibody or a fragment of one of the aforementioned antibodies directed against one of the aforementioned polypeptides or against a functional variant thereof, a vector comprising a nucleic acid coding for one of the aforementioned antibodies, a vector comprising a nucleic acid coding for one of the aforementioned antibody fragments, a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibodies, and a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibody fragments, is administered to the patient in need of a the treatment in a therapeutically effective amount.

[016] Another aspect of the invention is a pharmaceutical composition comprising at least one compound selected from the group consisting of a polypeptide according to the

invention, a functional variant thereof, a nucleic acid encoding one of the aforementioned polypeptides or a functional variant thereof, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the aforementioned vector, an antibody directed against one of the aforementioned polypeptides, an antibody directed against a functional variant of one of the aforementioned polypeptides, a fragment of one of the aforementioned antibodies, a vector comprising a nucleic acid coding for one of the aforementioned antibodies, a vector comprising a nucleic acid coding for one of the aforementioned antibody fragments, a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibodies, and a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibody fragments and, optionally, suitable additives or auxiliaries.

[017] The accession numbers of the polypeptides according to the invention and their cDNAs are shown in Table 2A to 2D.

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[047] **Table 2A to 2D: Polypeptides and cDNAs with their respective SEQ ID numbers and accession numbers from the GenBank database.**

[048]

Table 2A

Gene	Polypeptide (SEQ ID)	Accession number	DNA (SEQ ID)	Accession number
PI4K2	1	NP-060895	94	NM_018425
ZNF216	2	NP_005998	95	NM_006007
AKR1C1	3	NP_001344	96	NM_001353
dUT	4	NP_001939	97	NM_001948
PACE4	5	NP_002561	98	NM_002570
BIGH3	6	NP_000349	99	NM_000358
PRKAR1A	7	NP_002725	100	NM_002734
s.t. Ocia	8	NP_060300	101	NM_017830
SDCCAG28	9	NP_006636	102	NM_006645
PRDX1	10	NP_002565	103	NM_002574
TMP21	11	NP_006818	104	NM_006827
IQGAP2	12	NP_006624	105	NM_006633
Rab2	13	NP_002856	106	NM_002865
ARF1	14	NP_001649	107	NM_001658
HSPC1	15	NP_005339	108	NM_005348
TLR5	16	NP_003259	109	NM_003268
GAP-SH3	17	NP_005745	110	NM_005754
Crisp-3	18	NP_006052	111	NM_006061
TM4SF4	19	NP_004608	112	NM_004617

AQP9	20	NP_066190	113	NM_020980
LOC51716	21	NP_057364	114	NM_016280
Cystatin	22	NP_000091	115	NM_000100
Ki	23	NP_005780	116	NM_005789

[049]

[050]

[051]

Table 2B

Gene	Polypeptide (SEQ ID)	Accession number	DNA (SEQ ID)	Accession number
Porimin	24	NP_443164	117	NM_052932
PTPRZ1	25	NP_002842	118	NM_002851
Rab9 effector p40	26	NP_005824	119	NM_005833
RBap48	27	NP_005601	120	NM_005610
PABPC1	28	NP_002559	121	NM_002568
NF1/B2	29	NP_005587	122	NM_005596
RPL7	30	NP_000962	123	NM_000971
HNRPDL	31	NP_005454	124	NM_005463
OBCL6	32	novel	125	novel
SNRPG	33	NP_003087	126	NM_003096
KREV-1	34	NP_002875	127	NM_002884
DRB5	35	NP_003833	128	NM_003842
PKCI-1	36	NP_005331	129	NM_005340
IMPACT	37	NP_060909	130	NM_018439
BMI	38	NP_005171	131	NM_005180
G3BP	39	NP_005745	132	NM_005754
RHEB2	40	NP_005605	133	NM_005614
MARCKS	41	NP_002347	134	NM_002356
ALURBP	42	NP_003124	135	NM_003133
PPGB	43	NP_000299	136	NM_000308
GRB2	44	NP_002077	137	NM_002086

TRAP1	45	NP_057376	138	NM_016292
PDHB	46	NP_000916	139	NM_000925
DAD-1	47	NP_001335	140	NM_001344
PSME2	48	NP_002809	141	NM_002818
QP-C	49	NP_006285	142	NM_006294
MTRPS33	50	NP_444263	143	NM_053035

[052]

Table 2C

Gene	Polypeptide (SEQ ID)	Accession number	DNA (SEQ ID)	Accession number
ARF4	51	NP_001651	144	NM_001660
DDB1	52	NP_001914	145	NM_001923
GNG10	53	NP_004116	146	NM_004125
DP1	54	NP_002810	147	NM_002819
ATP1B1	55	NP_001668	148	NM_001677
SLC25A3	56	NP_002626	149	NM_002635
SNC6	57	NP_003923	150	NM_003932
OMG	58	NP_002535	151	NM_002544
PB1S	59	NP_002784	152	NM_002793
RPS21	60	NP_001015	153	NM_001024
MMP-2	61	NP_004521	154	NM_004530
YWHAZ	62	NP_663723	155	NM_145690
PPP3R1	63	NP_671709	156	NM_147180
CTNNA1	64	NP_001894	157	NM_001903
ADCYAP1	65	NP_001108	158	NM_001117
syntenin	66	NP_005616	159	NM_005625
topoisomerase IIb	67	NP_001059	160	NM_001068
UMP-CMPK	68	NP_057392	161	NM_016308
PSMD4	69	NP_722544	162	NM_153822
hu_BTF3	70	NP_001198	163	NM_001207
rhoA	71	NP_001655	164	NM_001664

LDH-B	72	NP_002291	165	NM_002300
TBXA2-R	73	NP_001051	166	NM_001060
hu_CAP	74	NP_006357	167	NM_006366
hu_PP2a-cat	75	NP_002706	168	NM_002715
SDHC	76	NP_002992	169	NM_003001

[053]

Table 2D

Gene	Polypeptide (SEQ ID)	Accession number	DNA (SEQ ID)	Accession number
hu_GDP-di2	77	NP_001166	170	NM_001175
CCNI	78	NP_006826	171	NM_006835
Mac25	79	NP_001544	172	NM_001553
TBP	80	NP_003185	173	NM_003194
FDX1	81	NP_004100	174	NM_004109
NLVCF	82	NP_003767	175	NM_003776
GNG3	83	NP_036334	176	NM_012202
RCN2	84	NP_002893	177	NM_002902
hu_adk2	85	NP_001616	178	NM_001625
hu_Dcsa19	86	NP_009035	179	NM_007104
c/EBP	87	NP_001797	180	NM_001806
Rab GG	88	NP_004573	181	NM_004582
**c-syn-1	89	NP_002028	182	NM_002037
**c-syn-2	90	NP_694592	183	NM_153047
**c-syn-3	91	NP_694593	184	NM_153048
PPP1R15A	92	NP_055145	185	NM_01433
SCL5A6	93	NP_066918	186	NM_021095

[054] [(**)c-syn represents three alternative nucleotide transcripts with corresponding three protein products]

[055]

[056] A subset of these nucleic acids according to the invention have been shown by RT-PCR analysis to be specifically expressed or deregulated in other cancers of epithelial origin and preferably not in corresponding normal human tissue(s). These nucleic acids

include SEQ ID Nos. 94 to 186 (provided in Table 2A to 2D). Deregulated nucleic acids in liver cancer may preferably be highly relevant to other cancers of the gastrointestinal tract as these tissues share a common embryological origin. Consequently, these nucleic acids and the encoded polypeptides may preferably be similarly utilized for diagnostics methods, pharmaceutical compositions and methods of prevention and/or treatment of these epithelial cancers.

[057] The polypeptides and nucleic acids according to the invention have in common that they are differentially expressed in a sample isolated from a patient suffering from a disorder according to the invention compared to a reference sample. The regulation of the polypeptides and nucleic acids according to the invention is essential for the pathologic process and which are thus in a direct or indirect relationship with diagnosis, prevention and/or treatment of disorders according to the invention. The polypeptides and the nucleic acids according to the invention do not belong to the targets known until now such that surprising and completely novel approaches for diagnosis and therapy result from this invention.

[058] Generally, the analysis of differentially expressed genes in tissues is less likely to result in errors in the form of artifactual false-positive clones than the analysis of cell culture systems. In addition to the fact that existing cell culture systems cannot adequately simulate the complexity of pathological processes in the tissue, the variations in cell behavior in the culture environment lead to nucleic acid and polypeptide expression patterns with questionable relation to the actual pathologic state. These problems may be less pronounced by an approach that utilizes gene expression in normal and diseased human tissue but again multiple variables confound clear identification of differential gene expression that is directly relevant to disease. For example, differentially expressed nucleic acids may result from inter-individual differences, metabolic state and/or clinical treatment paradigm. Further, large scale gene expression studies using cDNA microarrays do not indicate the cellular source of variation in gene expression. In addition, a differential gene expression study including all or most genes produces a very large volume of data that confounds identification of key disease-associated gene expression changes. Consequently, an approach that includes large scale profiling of gene expression from tissue from liver disorders that are defined only generally (as for example, "liver tumors") is unlikely to illuminate key genes involved in the disease process and it is these key genes that represent best targets for diagnostics and therapeutic intervention.

[059] On account of these difficulties, the success of the screening is significantly dependent on the choice of the experimental parameters. While the methods used are based on established procedures, the screening and verification strategy is already inventive *per se* owing to the elaborate and defined choice of parameters. A unique

approach employed in this invention utilizes discrete, pathologist-confirmed liver cancer pathologies for production of disease specific cDNA libraries enriched in nucleic acids specifically up- and down-regulated in HCC compared with a pool of non-neoplastic human livers. Non-diseased reference liver samples for the experiments are also diagnostically confirmed and pooled from 3 independent samples to reduce detection of false positives resulting from inter-individual variations. Nucleic acids commonly expressed at similar levels in the reference liver pool and in diseased liver (i.e., HCC) are removed by the generation of subtractive suppressive hybridization (SSH) cDNA libraries (Diatchenko et al., 1996, Proc. Natl. Acad. Sci. USA, 93:6025-6030). These cDNAs are highly enriched for nucleic acids both up- and down-regulated in HCC but do not represent those that are not differentially expressed. Each of several thousand SSH clones were amplified by the polymerase chain reaction (PCR) and affixed to glass slides in custom cDNA microarrays. RNA from additional pathologist-confirmed liver disorders is converted to fluorescently-labeled cDNA for competitive hybridization with the pooled non-diseased liver RNA on the microarrays. The resulting ratio of hybridization intensity reveals nucleic acids specifically deregulated in liver disorders. In addition to providing a pool of candidate cDNAs highly enriched for differentially expressed genes, the SSH library represents on a genome-wide scale most if not all differentially expressed genes with far fewer clones than in standard cDNA libraries. This feature thereby focuses on nucleic acids specifically deregulated in disease. The SSH libraries generated in this invention include cDNA clones from nucleic acids that are essentially not expressed in normal liver and thereby not represented in conventional cDNA libraries or on genome-scale cDNA microarrays.

[060] Overexpression of the sequences according to the invention in liver disorder tissue compared to normal liver is confirmed by independent analysis of RNA levels with sequence-specific quantitative RT-PCR (Q-PCR). In these verification experiments, PCR product corresponding to the cellular RNA levels of the sequences according to the invention are monitored by fluorescent detection of the specific PCR product. The fluorescent signal is provided either by a sequence specific hydrolysis probe oligonucleotide (primer) in the TaqMan/Assay-on-Demand procedure (Figure 100 to 103) or by a fluorescent double stranded DNA binding dye such as SYBR green (Figure 104). Levels of PCR products corresponding to the sequences according to the invention are normalized for experimental variability by comparison with the levels of 'housekeeping' genes including ß-actin, which are considered relatively invariant in disease or following experimental manipulations. The reference gene primers used for TaqMan Q-PCR analyses are GAPDH-p1, (SEQ ID 187); GAPDH-p2, (SEQ ID 188); GAPDH-p3, (SEQ ID 189); ßActin-p1, (SEQ ID 190); ßActin-p2, (SEQ ID 191); and

ßActin-p3, (SEQ ID 192). The reference gene primers used for SYBR Green analyses are ßActin-p4, (SEQ ID 193); and ßActin-p5, (SEQ ID 194). The determination of RNA levels relative to these housekeeping genes in Q-PCR experiments is performed according to the method of Pffafl (Nucleic Acids Research, 2001, 29(9):e45). These techniques are well known to a person skilled in the art.

[061] Furthermore, expression of HCC deregulated genes according to this invention correlates with proliferation of hepatoma cells (Hep3B, HepG2) following for example 8 hours and 12 hours serum stimulation of quiescent cells. This finding supports the suggestion that overexpression of the sequences according to the invention is functionally significant for proliferative liver disorders such as liver cancer.

[062] Compared to the state of the art, these polypeptides and nucleic acids surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis of the liver disorders and/or epithelial cancers. The nucleic acids and polypeptides according to the invention can be utilized for the diagnosis, prevention and treatment of liver disorders, and epithelial cancers.

[063] The present invention relates to at least one polypeptide comprising a sequence according to one of the SEQ ID 1 to SEQ ID 93, or a functional variant thereof. The invention also relates to a nucleic acid coding for the polypeptide or a functional variant thereof.

[064] In preferred embodiment the polypeptide consists of the sequence according to the SEQ ID 1. In another preferred embodiment the nucleic acid consists of the sequence according to the SEQ ID 94.

[065] Compared to the state of the art, these polypeptides and nucleic acids surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis of the liver disorders and/or epithelial cancers.

[066] In another aspect of the invention the invention relates to the use of at least one polypeptide according to the SEQ ID 1 to SEQ ID 93, a functional variant of the polypeptide, a nucleic acid encoding one of the aforementioned polypeptides, a nucleic acid encoding the functional variant, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the aforementioned vector, an antibody directed against one of the aforementioned polypeptides, an antibody directed against a functional variant of one of the aforementioned polypeptides, a fragment of one of the aforementioned antibodies, a vector comprising a nucleic acid coding for one of the aforementioned antibodies, a vector comprising a nucleic acid coding for one of the aforementioned antibody fragments, a

cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibodies, and/or at least one cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibody fragments, for the diagnosis, prevention and/or treatment of disorders according to the invention. Further embodiments of the invention are described in detail below.

[067] When compared to the state of the art of therapy of liver disorders, and/or epithelial cancers the use of these components surprisingly provide an improved, sustained and/or more effective diagnosis, prevention and/or treatment of disorders according to the invention.

[068] The term "polypeptide" refers to the full length of the polypeptide according to the invention. In a preferred embodiment the term "polypeptide" also includes isolated polypeptides and polypeptides that are prepared by recombinant methods, e.g. by isolation and purification from a sample, by screening a library and by protein synthesis by conventional methods, all of these methods being generally known to the person skilled in the art. Preferably, the entire polypeptide or parts thereof can be synthesized, for example, with the aid of the conventional synthesis such as the Merrifield technique. In another preferred embodiment, parts of the polypeptides according to the invention can be utilized to obtain antisera or specific monoclonal antibodies, which may be used to screen suitable gene libraries prepared to express the encoded protein sequences in order to identify further functional variants of the polypeptides according to the invention.

[069] The term "polypeptide according to the invention" refers to the polypeptides according to the SEQ ID 1 to SEQ ID 93 (Table 2A to 2D).

[070] The term "functional variants" of a polypeptide within the meaning of the present invention refers to polypeptides which have a sequence homology, in particular a sequence identity, of about 70%, preferably about 80%, in particular about 90%, especially about 95%, most preferred of 98 % with the polypeptide having the amino acid sequence according to one of the SEQ ID 1 to SEQ ID 93. Such functional variants are, for example, the polypeptides homologous to a polypeptide according to the invention, which originate from organisms other than human, preferably from non-human mammals such as, for example mouse, rats, monkeys and pigs. Other examples of functional variants are polypeptides that are encoded by different alleles of the gene, in different individuals, in different organs of an organism or in different developmental phases.

[071] Functional variants, for example, also include polypeptides that are encoded by a nucleic acid which is isolated from non-liver-tissue, e.g. embryonic tissue, but after expression in a cell involved in liver disorders have the designated functions. Functional variants preferably also include naturally occurring or synthetic mutations,

particularly mutations that quantitatively alter the activity of the peptides encoded by these sequences. Further, such variants may preferably arise from differential splicing of the encoding gene.

[072] "Functional variants" refer to polypeptides that have essentially the same biological funtion(s) as the corresponding polypeptide according to the invention. Such biological function can be assayed in a functional assay.

[073] In order to test whether a candidate polypeptide is a functional variant of a polypeptide according the invention, the candidate polypeptide can be analyzed in a functional assay generally known to the person skilled in the art, which assay is suitable to assay the biological function of the corresponding polypeptide according to the invention. Such functional assay comprise for example cell culture systems; enzymatic assays, the generation of mice in which the genes are deleted ("knocked out") or mice that are transgenic for gene encoding the candidate polypeptide, etc. If the candidate polypeptide demonstrates or directly interferes with essentially the same biological function as the corresponding polypeptide according to the invention, the candidate polypeptide is a functional variant of the corresponding polypeptide, provided that the candidate polypeptide fulfills the requirements on the level of % sequence identity mentioned above.

[074] Furthermore, the term "functional variant" encompasses polypeptides that are preferably differentially expressed in patients suffering from liver disorders, or other epithelial cancers relative to a reference sample or a reference library, including polypeptides expressed from mutated genes or from genes differentially spliced, provided that the candidate functional variant polypeptide fulfills the criteria of a functional variant on the level of % sequence identity. Such expression analysis can be carried out by methods generally known to the person skilled in the art.

[075] "Functional variants" of the polypeptide can also be parts of the polypeptide according to the invention with a length of at least from about 7 to about 1000 amino acids, preferably of at least 10 amino acids, more preferably at least 20, most preferred at least 50, for example at least 100, for example at least 200, for example at least 300, for example at least 400, for example at least 500, for example at least 600 amino acids provided that they have essentially the same biological function(s) as the corresponding polypeptide according to the invention. Functional variants, such as in fusion proteins, may contain either on one or both ends additional aminoacid stretch(es), preferably 1 to 50 amino acids, more preferably 20 amino acids. Also included are deletions of the polypeptides according to the invention, in the range from about 1-30, preferably from about 1-15, in particular from about 1-5 amino acids provided that they have essentially the same biological function(s) as the corresponding polypeptide according to the invention. For example, the first amino acid

methionine can be absent without the function of the polypeptide being significantly altered. Also, post-translational modifications, for example lipid anchors or phosphoryl groups may be present or absent in variants.

[076] "Sequence identity" refers to the degree of identity (% identity) of two sequences, that in the case of polypeptides can be determined by means of for example BLASTP 2.0.1 and in the case of nucleic acids by means of for example BLASTN 2.014, wherein the Filter is set off and BLOSUM is 62 (Altschul et al., 1997, Nucleic Acids Res., 25:3389-3402).

[077] "Sequence homology" refers to the similarity (% positives) of two polypeptide sequences determined by means of for example BLASTP 2.0.1 wherein the Filter is set off and BLOSUM is 62 (Altschul et al., 1997, Nucleic Acids Res., 25:3389-3402).

[078] The term "liver disorder" refers to and comprises all kinds of disorders that preferably affect the anatomy, physiology, metabolic, and/or genetic activities of the liver, that preferably affect the generation of new liver cells, and/or the regeneration of the liver, as a whole or parts thereof preferably transiently, temporarily, chronically or permanently in a pathological way. Preferably also included are inherited liver disorders and neoplastic liver disorders. Liver disorder is further understood to preferably comprise liver disorders caused by trauma, intoxication, in particular by alcohol, drugs or food intoxication, radiation, infection, cholestasis, immune reactions, and by inherited metabolic liver diseases. Preferred examples of liver disorders include cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's Disease, and haemochromatosis. Preferably further included are autoimmune-disorders wherein the autoimmune response is directed against at least one polypeptide according to the invention. Within the meaning of the present invention the term "liver disorder" preferably also encompasses liver cancer, for example hepatocellular carcinoma (HCC), benign liver neoplasms such as adenoma and/or FNH. Preferably HCC further comprises subtypes of the mentioned disorders, preferably including liver cancers characterized by intracellular proteinaceous inclusion bodies, HCCs characterized by hepatocyte steatosis, and fibrolamellar HCC. For example, precancerous lesions are preferably also included such as those characterized by increased hepatocyte cell size (the "large cell" change), and those characterized by decreased hepatocyte cell size (the "small cell" change) as well as macro regenerative (hyperplastic) nodules (Anthony, P. in MacSween et al, eds. Pathology of the Liver, 2001, Churchill Livingstone, Edinburgh).

[079] The term "epithelial cancer" within the meaning of the invention includes adenocarcinomas of any organ other than the liver, preferably of the lung, stomach, kidney, colon, prostate, skin and breast, and refers to disorders of these organs in which epithelial cell components of the tissue are transformed resulting in a malignant tumor

identified according to the standard diagnostic procedures as generally known to a person skilled in the art.

[080] Within the meaning of the invention the term "disorder according to the invention" encompasses epithelial cancer and liver disorders as defined above.

[081] In the case of polypeptides, the term "differential expression of a polypeptide" refers to the relative level of expression of the polypeptide in an isolated sample from a patient compared to the expression of the polypeptide in a reference sample or a reference library. The expression can be determined by methods generally known to the person skilled in the art. Examples of such methods include immunohistochemical or immunoblot or ELISA detection of the polypeptide with antibodies specific for the polypeptide. Detection of the polypeptide through genetic manipulation to label the polypeptide and detection in a model system is preferably also included such as by tagging the polypeptide in a transgene for expression in a model system.

[082] The term "sample" refers to a biomaterial comprising liver tissue or liver cells, also tissue from another organ subject to malignant transformation or a cell from this organ, blood, serum, plasma, ascitic fluid, pleural effusions, cerebral spinal fluid, saliva, urine, semen or feces.

[083] The sample can be isolated from a patient or another subject by means of methods including invasive or non-invasive methods. Invasive methods are generally known to the skilled artisan and comprise for example isolation of the sample by means of puncturing, surgical removal of the sample from the opened body or by means of endoscopic instruments. Minimally invasive and non-invasive methods are also known to the person skilled in the art and include for example, collecting body fluids such as blood, serum, plasma, ascitic, pleural and cerebral spinal fluid, saliva, urine, semen, and feces. Preferably the non-invasive methods do not require penetrating or opening the body of a patient or subject through openings other than the body openings naturally present such as the mouth, ear, nose, rectum, urethra, and open wounds.

[084] The term "minimally invasive" procedure refers to methods generally known, especially by persons skilled in the art, for obtaining patient sample material that do preferably not require anesthesia, can be routinely accomplished in a physician office or clinic and are either not painful or only nominally painful. The most common example of a minimally invasive procedure is venupuncture.

[085] The term "reference sample" refers to a sample that serves as an appropriate control to evaluate the differential expression of a nucleic acid and/or a polypeptide according to the invention in a given sample isolated from a patient; the choice of such appropriate reference sample is generally known to the person skilled in the art. Examples of reference samples include samples isolated from a non-diseased organ or tissue or cell(s) of the same patient or from another subject, wherein the non-diseased

organ or tissue or cell(s) is selected from the group consisting of liver tissue or liver cells, blood, or the samples described above. For comparison to expression in the sample isolated from a patient with the liver disorder, the reference sample may also include a sample isolated from a non-diseased organ or tissue or cell(s) of a different patient, wherein the liver disordered- tissue or cell(s) is selected from the sample group listed above. Moreover the reference may include samples from healthy donors, preferably matched to the age and sex of the patient.

[086] The term "reference library" refers to a library of clones representing expressed genes, which library is preferably prepared from non-diseased liver tissue or cells. The reference library may also derive from mRNA from non-diseased liver tissue or cells and may also comprise a data base comprising data on non-diseased tissue expression of nucleic acids. For comparison of the expression of the nucleic acids or polypeptides according to the invention in a sample isolated from a patient with the disordered liver, the reference library may comprise an expression library prepared from liver disorder-diseased liver tissue or cells and a data base comprising data on liver disorder-specific expression of nucleic acids.

[087] The term "patient" within the meaning of the invention includes animals, preferably mammals, and humans, dead or alive. The patient is either suffering from a liver disorder, and/or other epithelial cancer, subject to analysis, preventive measures, therapy and/or diagnosis in the context of liver disorder and/or other epithelial cancer.

[088] The term "subject" within the meaning of the invention includes animals, preferably mammals, and humans, dead or alive that is not suffering from a liver disorders and/or other epithelial cancer and thus represent a preferred appropriate control for the determination of differential expression of nucleic acids and/or polypeptides according to the invention in a patient.

[089] The term "effective treatment" within the meaning of the invention refers to a treatment that preferably cures the patient from at least one disorder according to the invention and/or that improves the pathological condition of the patient with respect to at least one symptom associated with the disorder, preferably 3 symptoms, more preferably 5 symptoms, most preferably 10 symptoms associated with the disorder; preferably on a transient, short-term (in the order of hours to days), long-term (in the order of weeks, months or years) or permanent basis, wherein the improvement of the pathological condition may be preferably constant, increasing, decreasing, continuously changing or oscillatory in magnitude as long as the overall effect is a significant improvement of the symptoms compared with a control patient. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50} may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio

LD_{50}/ED_{50}. Pharmaceutical compositions that exhibit large therapeutic indexes are preferred. The dose must be adjusted to the age, weight and condition of the individual patient to be treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

[090] The actual dosage depends on the nature and severity of the disorder being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated, that pharmaceutical compositions comprising of from about 0.1 to 500 mg of the active ingredient per individual dose, preferably of from about 1 to 100 mg, most preferred from about 1 to 10 mg, are suitable for therapeutic treatments.

[091] The active ingredient may be administered in one or several dosages per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 mg/kg intravenously (i.v.) and 1 mg perorally (p.o.). Preferred ranges are from 0.1 mg/kg/day to about 10 mg/kg /day i.v. and from 1 mg/kg/day to about 100 mg/kg/day p.o.

[092] In another aspect the invention relates to a fusion protein comprising a polypeptide according to the SEQ ID 1 to 93, or a functional variant thereof.

[093] A "fusion protein" refers to a polypeptide comprising at least one polypeptide according to the SEQ ID 1 to SEQ ID 93, a functional variant or part thereof and at least one component A selected from polypeptide, peptide and/or peptide analogue that is linked to the polypeptide according to the invention by means of covalent or non-covalent binding such as e.g. hydrogen bonds, generally known to the person skilled in the art. Preferred examples of component A for fusion proteins are polypeptide, peptide and/or peptide analogues that facilitate easier detection of the fusion proteins; these are, for example, "green-fluorescent-protein", or variants thereof. Also included are fusion proteins that facilitate purification of the recombinant protein such as "His-tags", or fusions that increase the immunogenicity of the protein.

[094] Fusion proteins according to the invention can be produced by methods generally known to the person skilled in the art. The fusion proteins according to the invention can be used for the diagnosis, prevention and or treatment of liver disorders and/or epithelial cancer.

[095] Compared to the state of the art, these fusion proteins surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis and/or improved, sustained and/or more effective treatment of the liver disorders and/or epithelial cancers.

[096] Preferred nucleic acids according to the invention comprise a sequence according to one of SEQ ID 94 to SEQ ID 186, or a variant thereof. In particular the invention

relates to nucleic acids according to the invention that have been isolated.

[097] Compared to the state of the art, these nucleic acids and polypeptides surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis and/or improved, sustained and/or more effective treatment of the liver disorders and/or epithelial cancers.

[098] The term "nucleic acid according to the invention" refers to the nucleic acids corresponding to the SEQ ID 94 to SEQ ID 186 and/or variants thereof.

[099] The term "encoding nucleic acid" relates to a DNA sequence that codes for an isolatable bioactive polypeptide according to the invention or a precursor thereof. The polypeptide can be encoded by a sequence of full length or any part of the coding sequence as long as the biological function, such as for example receptor-activity, is essentially retained (cf. definition of functional variant).

[100] It is known that small alterations in the sequence of the nucleic acids described above can be present, for example, due to the degeneration of the genetic code, or that untranslated sequences can be attached to the 5' and/or 3' end of the nucleic acid without significantly affecting the activity of the encoded polypeptide. This invention, therefore, also comprises so-called naturally occurring and artificially generated "variants" of the nucleic acids described above.

[101] Preferably, the nucleic acids used according to the invention are DNA or RNA, preferably a DNA, in particular a double-stranded DNA. In particular the nucleic acid according to the invention may be an RNA molecule, preferably single-stranded or a double-stranded RNA molecule. The sequence of the nucleic acids may further comprise at least one intron and/or one polyA sequence.

[102] Nucleic acids according to the invention can be produced by methods generally known to the skilled artisan and have also been described in detail below.

[103] "Variant" within the meaning of the invention refers to all DNA sequences that are complementary to a DNA sequence, which hybridize with the reference sequence under stringent conditions and have a similar activity to the corresponding nucleic acid according to the invention. The nucleic acids according to the invention can also be used in the form of their antisense sequence.

[104] "Variant" of the nucleic acids can also be homologues from other species with sequence identity preferably 80%, in particular 90%, most preferred 95%.

[105] "Variant" of the nucleic acids can also be parts of the nucleic acid according to the present invention with at least about 8 nucleotides length, preferably with at least about 16 nucleotides length, in particular with at least about 21 nucleotides length, more preferably with at least about 30 nucleotides length, even more preferably with at least about 40 nucleotides length, most preferably with at least about 50 nucleotides length as long as the parts have a similar activity to the corresponding polypeptide according

to the invention. Such a functional activity of an expressed polypeptide encoded by such a nucleic acid can be assayed using the functional assays described further above.

[106] In a preferred embodiment of the invention the nucleic acid comprises a nucleic acid having a sequence complementary to a nucleic acid according to the invention, or a variant thereof. Preferably the nucleic acid comprises a non-functional mutant variant of the nucleic acid according to the invention, or a variant thereof.

[107] In particular the invention relates to a nucleic acid having a complementary sequence wherein the nucleic acid is an antisense molecule or an RNA interference molecule.

[108] The term "non-functional mutant variant of a nucleic acid" refers to a nucleic acid derived from a nucleic acid according to the invention, or a variant thereof having been mutated such that the polypeptide encoded by the non-functional mutant variant of the nucleic acid exhibits a biological activity which in comparison the non-mutated polypeptide is significantly decreased or abolished. Such activity of the polypeptide encoded by the non-functional mutant variant nucleic acid can be determined by means of a functional assay as described above for the evaluation of functional variants. The construction and screening of such non-functional mutant variant derived from a nucleic acid according to the invention are generally known to the person skilled in the art. Such "non-functional mutant variant of a nucleic acid" according to the invention can be expressed in a patient and will preferably abolish or diminish the level of expression of the targeted nucleic acid by competing with the native mRNA molecules for translation into polypeptides by the ribosomes.

[109] "Stringent hybridization conditions" refer to those conditions in which hybridization takes place at 60°C in 2.5 xSSC buffer and remains stable following a number of washing steps at 37°C in a buffer of lower salt concentration.

[110] The term "differential expression of a nucleic acid" refers to the relative level of expression of the nucleic acid in an isolated sample from a patient compared to the expression of the nucleic acid in a reference sample or a reference library. Definitions of reference samples and reference libraries have been described in detail above. The expression can be determined by methods generally known to the person skilled in the art. Examples of such methods include RNA blot (northern) analysis, nuclease protection, in situ hybridization, reverse transcriptase PCR (RT-PCR; including quantitative kinetic RT-PCR). cDNA and oligonucleotide microarrays are also included as such methods.

[111]

[112] Preferred embodiment of the invention relates to the HCC up-regulated phosphatidylinositol 4-kinase type II (PI4K2) polypeptide (Accession. No. NP_060895, SEQ ID 1) and to the nucleic acid PI4K2 (Accession. No. NM_018425, SEQ ID 94)

coding for the polypeptide. The prevalent phosphatidylinositol (PtdIns) phosphate kinase activity in many mammalian cell types is conferred by the widespread type 2 kinase (PI4K2). The human type 2 isoform has been partially purified from plasma membrane rafts of human A431 epidermoid carcinoma cells. (Minogue S. et al., 2001. J Biol Chem., 18; 276(20):16635-40. Epub 2001 Feb 13). The predicted amino acid sequence revealed two isoforms: 2alpha and 2beta. The type 2alpha mRNA appears to be expressed ubiquitously in human tissues, and homologues appear to be expressed in all eukaryotes, but the gene encoding this PtdIns family member, however, has not previously been reported to be expressed at elevated levels in disorders according to the invention, in particular in HCC.

[113] Expression of this mRNA is elevated on average almost 2-fold relative to non-diseased liver in 46% of the HCC cases profiled (see Figure 1, Table 3A). Elevated expression of the encoding mRNA is also evident in FNH (to even a higher extent than in HCC; Figure 9/Table 4A), but not in cirrhotic livers subjected to this cDNA microarray expression profiling procedure (Figure 9 and Table 3A). For this and the other nucleic acids according to the invention, this value for expression includes the expression value ratio data from all of the (28) HCC samples subjected to the cDNA microarray expression profiling experiments, including the values from samples that are not elevated by 2-fold or greater.

[114] These results should confirm that the differential upregulated expression of the PI4K2 cDNA sequence is highly specific for disorders according to the invention. Therefore the PI4K2 polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis, prevention and treatment of disorders according to the invention

[115] In another preferred embodiment the nucleic according to the invention is the Zinc finger protein 216, ZNF216 cDNA (SEQ ID 95) which includes the open reading frame encoding ZNF216 polypeptide (SEQ ID 2). The ZNF216 polypeptide (GenBank sequence NP_005998) is another embodiment of the invention. The ZNF216 gene is identical to the already reported cochlear-expressed gene (Scott DA. et al., 1998, Gene, 215(2): 461- 469) that maps to the DFNB7/11 interval for autosomal recessive non-syndromic hearing loss (ARNSHL) located on human chromosome 9q13-q21. Although ZNF216 gene is highly conserved between human and mouse, containing two regions that show homology to the putative zinc finger domains of other proteins, the polypeptide sequence has unknown function. Based on homology to bovine cDNA tag A2, ZNF216 may play a role in development of vessel endothelium from precursor cells suggesting a potential regulatory role in neovascularization. In this line it was recently suggested that ZNF216 and its A20-like zinc finger domain (ZnF-A20) have redundant and distinct role in regulating NF-kappaB activation and apoptosis (Huang J, published online ahead of print January 30, 2004, J. Biol. Chem,

10.1074/jbc.M309491200). The gene encoding this zinc finger family member, however, has not previously been reported to be expressed at elevated levels in disorders according to the invention, in particular in HCC.

[116] The expression in HCC of RNA corresponding to assembled sequence SEQ ID 95 is confirmed experimentally. The initial sequence upregulated in HCC relative to non-diseased liver identified as an SSH cDNA clone corresponds to GenBank sequence NM_006007. The expression of sequences of this clone has not previously been reported in liver or in HCC.

[117] In a preferred embodiment the polypeptide according to the invention is the ZNF216 polypeptide (SEQ ID 2) which is surprisingly identified from an mRNA identified to be upregulated in HCC by an average of 16-fold relative to non-diseased liver (Figure 1) in 54% of the profiled cases (Table 3A). Similarly, elevated expression of the encoding mRNA relative to non-diseased liver is also evident in FNH but not in cirrhotic livers (see Figure 10, Tables 4A/5A).

[118] cDNA sequences encoding this polypeptide and overlapping with this mRNA might be identified with reverse transcriptase PCR analysis and these nucleic acids can be similarly elevated in HCC. Furthermore, high expression specificity of the ZNF216 cDNA can be confirmed by quantitative assessment (Q-PCR) in HCC, FNH and Cirrhosis in comparison to expression pattern in normal tissue(s). The TaqMan procedure utilizing the parallel examination of both GAPDH and ß-actin as reference genes should verify a large over expression of ZNF216 cDNA (SEQ ID 95) in HCC when compared to FNH and Cirrhosis. For TaqMan analyses ZNF 216 expression might be determined with gene specific oligonucleotide primers including ZNF216-p1, 5'-gagaggacaaaataactaccc-3', SEQ ID 195 (from nucleotide 611- 631 of SEQ ID 95 forward strand), ZNF216-p2, 5'-caattcaggagctttttcttca-3', SEQ ID 196 (from nucleotide 726-705 of SEQ ID 95 reverse strand) and the "hydrolysis" probe ZNF216-pr, 5'-tactgggctgagaaactgatggactgggctga-3' SEQ ID 198 (from nucleotide 694-663 of SEQ ID 95 reverse strand).

[119] Furthermore, the expression of this HCC-deregulated gene correlates with proliferation of hepatoma cells, showing 2-fold and 3-fold increase of ZNF216 mRNA in Hep3B cell line upon 8 hours and 12 hours serum stimulation of quiescent cells, respectively (see Figure 106).

[120] These results demonstrate that ZNF216 polypeptide (SEQ ID 2) and the nucleic acid encoding the polypeptide (SEQ ID 95) can be employed in the prevention and therapy of disorders according to the invention, in particular for the treatment of hyperplastic (including neoplastic) liver diseases. With regard to the treatment it is preferred to carry out the treatment such that the expression of the ZNF216 polypeptide or of the nucleic acid encoding the polypeptide is reduced and/or inhibited,

for example by administering antisense oligonucleotides or RNA interference molecules that specifically interact with the nucleic acid encoding the ZNF216 polypeptide. Alternatively the treatment may be carried out such that the activity of the ZNF216 polypeptide is reduced and/or inhibited, for example by administering an antibody directed against the ZNF216 polypeptide or an antibody fragment thereof which block the activity of the ZNF216 polypeptide to a patient in need of such treatment. Compared to the state of the art, this ZNF216 polypeptide and/or ZNF216 nucleic acid surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis and/or improved, sustained and/or more effective.

[121] In another preferred embodiment the nucleic acid according to the invention is the AKR1C1 nucleic acid (SEQ ID 96) that represents the sequence of an HCC deregulated cDNA clone. This gene encodes the Aldo-keto reductase family 1 member C1 sharing high sequence identity with three other gene members and is localized at chromosome 10p15-p14 (Stolz, A. et al, 1993, J. Biol. Chem., 268: 10448-10457). These enzymes catalyze the conversion of aldehydes and ketones to their corresponding alcohols by utilizing NADH and/or NADPH as cofactors. The enzymes display overlapping but distinct substrate specificity and may assist in the rapid intracellular transport of bile acids from the sinusoidal to the canalicular pole of the cell, and thereby having a role in monitoring the intrahepatic bile acid concentration. The AKR1C1 regulates progesterone action by converting the hormone into its inactive metabolite 20 alpha-hydroxyprogesterone, and toxicologically this enzyme activates polycyclic aromatic hydrocarbon trans-dihydrodiols to redox-cycling o-quinones. However, the significance of its potent induction by Michael acceptors and oxidative stress is unknown (Burczynski ME. et al., J Biol Chem., 2001, 276(4): 2890- 2897). Expression of sequences corresponding to this clone has been already reported in several tissues (including liver) and some tumors (including prostate, breast; e.g., Wiebe JP and Lewis MJ., 2003, BMC Cancer, 3(1): 9) but the sequence has not previously been described to be upregulated in HCC.

[122] In liver samples from HCC patients expression of the mRNA encoding this polypeptide is surprisingly elevated relative to non-diseased liver by an average value of 7-fold in 79% cases profiled (Figure 1, Table 3A). Elevated expression of the encoding mRNA relative to non-diseased liver is also evident in FNH but not in cirrhotic livers (Figure 11, Table 4A/5A).

[123] Independent RT-PCR analysis of expression levels of AKR1C1 mRNA in HCC relative to normal liver are determined with gene specific oligonucleotide primers including: AKR1C1-p1, 5'- ttggaaaggtcactgaaaaatct-3' (SEQ ID 199) and AKR1C1-p2, 5'-gctggctgcggttgaagttgg-3' (SEQ ID 200) verifying the specific expression of this gene (SEQ ID 96) in HCCs when compared to normal liver samples (Figure 104).

[124] Furthermore, the expression of this HCC-deregulated mRNA is showing 2-fold and 5-fold increase by serum stimulation of quiescent hepatoma cells (HepG2) upon 8 hours and 12 hours, respectively (Figure 107).

[125] The target gene encoded polypeptide enzymatic activity clearly shows the correlation between the upregulation of AKR1C1 gene transcript in HCC with the approximately 2-fold induction of the AKR1C1 enzymatic activity suggesting that elevated expression of this sequence is correlated with human liver tumor cell proliferation (Table 9).

[126] In yet another preferred embodiment the nucleic acid according to the invention is the dUTP pyrophosphatase, dUT nucleic acid (SEQ ID 97) which has been disclosed before (Accession. No NM_001948) encoding the dUT polypeptide (Accession. No NP_001939, SEQ ID 4). dUTP pyrophosphatase involved in nucleotide metabolism produces dUMP (through hydrolysis of dUTP), the immediate precursor of thymidine nucleotides and decreases the intracellular concentration of dUTP so that uracil cannot be incorporated into DNA (McIntosh E.M.et al., 1992; PNAS, 89: 8020-8024). Nuclear DUT- DUT-N (18 kDa) and mitochondrial DUT-M (23 kDa) isoforms of the protein have been identified in humans and arise from the same gene by the alternative use of 5' exons. DUT-N protein and mRNA levels are tightly regulated to coincide with DNA replication. DUT-N is phosphorylated by cyclin-dependent kinases (Ladner R.D., 1996, J. Biol. Chem., 271: 7745-7751). Recently, it has been shown that these isoforms are aberrantly expressed in some cancers (Pugacheva E.N. et al., 2002, Oncogene, 21(30): 4595- 4600) but the geneencoding these isoforms has not previously been reported to be expressed at elevated levels in HCC.

[127] Expression of the mRNA encoding the dUT polypeptide is induced by an average of 7-fold relative to non-diseased liver in 47% of the HCC cases profiled (Figure 1, Table 3A). Similarly, elevated expression of the encoding mRNA is also evident in FNH by an average 10.6-fold induction relative to non-diseased liver in 40% of the FNH cases profiled but not in the cirrhotic livers (Figure 12, Tables 4A/5A).

[128] Independent RT-PCR analyses of expression levels of dUT mRNA might be determined with gene specific oligonucleotide primers including primers for TaqMan analysis, for example: dUT-p1: 5'-ccgcgggctacgacctg-3', SEQ ID 201 (from nucleotide 153-169 of the SEQ ID 97 forward strand), dUT-p2, 5'-agccactcttccataacacc-3', SEQ ID 202 (from nucleotide 268-249 of the SEQ ID 97 reverse strand) and fluorescently-labeled probe dUT-pr, 5'-tgtccgttttcacaacagctttctccataggt-3', SEQ ID 203 (spanning bases from 227-197 of the SEQ ID 97 reverse strand).

[129] Furthermore, a specific high-affinity inhibitor blocks proliferation of hepatoma cells (Hep3B/HepG2); the specific small molecule inhibitor (DMT-dU (5'-O-(4,4'-Dimethoxytrityl)-2'-deoxyuridine; Sigma; No. D7279) (Persson, T. et al.,

1996, Bioorg. Med. Chem., 4: 553-556) stimulates a cytostatic and anti-proliferative response (Figures 108 to 109) in these cells.

[130] These results should confirm that the differential upregulated expression of the dUT cDNA sequence is highly specific for disorders according to the invention. Therefore the dUT polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis, prevention and treatment of disorders according to the invention.

[131] Another preferred embodiment of the invention relates to the HCC up-regulated Paired basic amino acid cleaving enzyme 4, PACE4 polypeptide (Accession. No. NP_002561, SEQ ID 5) and to the nucleic acid PACE4 (Accession. No. NM_002570, SEQ ID 98) coding for the polypeptide. The protein encoded by this gene belongs to the subtilisin/kexin-like proprotein convertase family while representing a calcium-dependent serine endoprotease that can efficiently cleave precursor proteins at their paired basic amino acid processing sites [consensus site: RX(K/R)R]. Expression of this gene has been already reported in several tissues (including liver) and suggested to play a role in tumor progression (in colon cancer, e.g. Khatib AM. et al., J Biol Chem., 2001, 276(33):30686-30693), but the sequence has not previously been described to be upregulated in HCC.

[132] Expression of this mRNA is elevated on average by 24-fold relative to non-diseased liver in 57% of the HCC cases profiled (see Figure 1, Table 3A). Elevated expression of the encoding mRNA is also evident in FNH (to a lesser extent than in HCC; Figure 13/Table 4A), but not in cirrhotic livers subjected to this cDNA microarray expression profiling procedure (Figure 13 and Table 5A).

[133] Taqman RT-PCR analyses of expression levels of PACE4 mRNA (Assay ID Catalogue Number: Hs00159844_m1, Applied Biosystems, USA, see Table 6) verify and confirm the specific elevation of the PACE4 cDNA (Figure 3A) showing up-regulation in 7/17 HCCs, 3/3 FNHs, in 3/3 Cirrhosis and in 0/3 non-neoplastic livers (NNL).

[134] Furthermore, the expression of this HCC-deregulated mRNA is showing 2.4-fold and 6.7-fold increase by serum stimulation of quiescent hepatoma cells (HepG2) upon 8 hours and 12 hours, respectively (Figure 107).

[135] These findings suggest a functionally significant role for PACE4 in disorders according to the invention, especially in HCC. Therefore the PACE4 polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis, prevention and treatment of disorders according to the invention.

[136] In another preferred embodiment invention relates to the HCC up-regulated Transforming growth factor ßeta-induced I, BIGH3 polypeptide (Accession number NP_000349; SEQ ID 6) and to the nucleic acid BIGH3 (Accession number NM_000358; SEQ ID 99) coding for the polypeptide. cDNA corresponding to this

mRNA has been identified in cDNA libraries expressed in many tissues but at low levels; and highly expressed in the corneal epithelium. This gene known to be induced by TGF-beta binds specifically to collagens and may regulate cell adhesion (Skonier J. et al., 1994, DNA Cell Biol., 6: 571- 584). BIGH3 gene has been shown to be up-regulated in oesophageal adenocarcinoma tissue (Hourihan RN. et al., 2003, Anticancer Res., 23(1A):161-5), but the sequence has not previously been reported to be up-regulated in disorders according to the invention, in particular in HCC.

[137] Expression of this mRNA is elevated on average by 5-fold relative to non-diseased liver in 79% of the HCC cases profiled (see Figure 1 and Table 3A). Similar analysis reveals elevated expression of this mRNA in 80% of the FNH cases profiled (Figure 14/Table 4A).

[138] The HCC induction of the BIGH3 gene is then verified by amplification of the sequence from the cDNA with primer pairs specific to BIGH3 nucleic acid (Assay ID Catalogue Number: Hs00154671_m1) in the Assay-On-Demand (Applied Biosystems, USA) quantitative PCR method and also confirming that the BIGH3 mRNA is not deregulated in cirrhosis (Figure 100).

[139] These findings suggest that the BIGH3 polypeptide and/or a functional variant thereof and/or the encoding nucleic acid and/or a variant thereof can be utilized for the diagnosis, prevention and treatment of disorders according to the invention (in particular for the diagnosis of in HCC and FNH).

[140] In another preferred embodiment the polypeptide according to the invention is the PRKAR1A polypeptide (Accession number NP_002725; SEQ ID 7) which is surprisingly identified from an mRNA identified to be upregulated in HCC (Accession number NM_002734; SEQ ID 100). PRKAR1A, a critical component of the cAMP signaling pathway represents a type I regulatory alpha subunit of cAMP-dependent protein kinase, suggested as a dominant negative regulator of transcription in somatic cell hybrids (Sandberg, M. et al., 1987, Biochem. Biophys. Res. Commun., 149:939-945). The inactive form of the enzyme is composed of two regulatory chains and two catalytic chains. Activation by cAMP produces two active catalytic monomers and a regulatory dimer that binds four cAMP molecules (Jones, K.W. et al., 1991, Cell, 66:861-872). Structural information of the protein is not yet obtained. PRKAR1A is likely to be expressed in many tissues. However, the sequence has not previously been reported to be up-regulated in disorders according to the invention, in particular in HCC.

[141] The mRNA encoding this polypeptide is elevated an average of 3-fold relative to non-diseased liver in 39% HCCs profiled (see Figure 1 and Table 3A) and similarly in FNH, but not in cirrhotic livers (Figure 15 and Tables 4A/5A).

[142] Independent verification analyses of expression levels of PRKAR1A mRNA might

be determined with gene specific oligonucleotide primers including, for example primer pairs specific to PRKAR1A nucleic acid (Assay ID Catalogue Number: Hs0000267597_m1) in the Assay-On-Demand (Applied Biosystems, USA) quantitative PCR method.

[143] These results suggest that the strongly upregulated expression of the PRKAR1A cDNA sequence is highly specific for disorders according to the invention, especially in HCC and FNH. Therefore the PRKAR1A polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis, prevention and treatment of disorders according to the invention.

[144] In a further preferred embodiment the invention relates to the s.t. Ocia nucleic acid (Accession number NM_017830; SEQ ID 101) coding for the Ovarian carcinoma immunoreactive antigen, s.t. Ocia polypeptide (Accession number NP_060300; SEQ ID 8) which may be expressed at low levels in many tissues and known to be elevated in ovarian cancer (Luo LY. et al., 2001,Biochem Biophys Res Commun., 12; 280(1): 401- 406). The gene encoding this putative tumor antigen, however, has not previously been described in liver cancer and not being reported to be expressed at elevated levels in disorders according to the invention, in particular in HCC.

[145] The mRNA encoding this polypeptide is elevated an average of 2.4-fold relative to non-diseased liver (NL) in 32% HCCs profiled (Figure 1 and Table 3A).mRNA levels are marginally elevated in FNH relative to non-diseased liver(Figure 16 and Table 4A). This mRNA is otherwise detected only infrequently in normal and cirrhotic livers subjected here to expression profiling.

[146] Independent RT-PCR analyses of expression levels of s.t.Ocia mRNA are determined with gene specific oligonucleotide primers (Assay ID Catalogue Number: Hs00215197_m1, Applied Biosystems, USA) in the Assay-On-Demand quantitative PCR method confirming that the s.t.Ocia mRNA is not deregulated in cirrhosis (Figure 101/ Table 6).

[147] These results suggest that the upregulated expression of the s.t.Ocia cDNA sequence is highly specific for disorders according to the invention, especially HCC. Therefore the s.t.Ocia polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis,prevention and treatment of disorders according to the invention, in particular for the diagnosis of HCC and FNH.

[148] In yet another preferred embodiment the invention relates to the serologically defined colon cancer antigen 28, SDCCAG28 nucleic acid (Accession number NM_006645; SEQ ID 102). The cDNA clones corresponding to the SDCCAG28 mRNA have been identified in many tissues including colon and other cancers (Scanlan, M.J. et al., 1998, Int. J. Cancer, 76:652-658), but neither this mRNA nor the encoded polypeptide have been previously implicated in disorders according to the

invention, in particular in liver disorders or in HCC. The invention further relates to the polypeptide encoding for the SDCCAG28, a predicted polypeptide of 40.5 kDa (SDCCAG28, SEQ ID 9; NP_006636 in the GenBank database). The presence of this polypeptide has not been described in any cell or tissue and its function has not been reported, primary sequence suggests similarity to phosphatidylcholine transfer protein 2 (Lai,C.-H., 2000, Genome Res., 10: 703- 713).

[149] mRNA encoding this polypeptide is elevated an average 3-fold in 71% of the HCCs examined and similarly by nearly 7-fold in FNH (40% cases), all relative to non-diseased liver (Figures 1 and 17, Tables 3A/ 4A).

[150] Independent RT-PCR analyses of expression levels of SDCCAG28 mRNA are determined with gene specific oligonucleotide primers (Assay ID Catalogue Number: Hs00246405_m1) as described for the BIGH3 gene, confirming that the SDCCAG28 mRNA is not deregulated in cirrhosis (Figure 3B). The Assay-on-Demand Q-PCR shows upregulation in 8/17 HCCs, 2/3 FNHs, 1/3 Cirrhosis and 0/3 NNL of profiled cases.

[151] Additionaly, expression of this HCC-deregulated gene correlates with proliferation of hepatomacells, showing almost 2-fold and 4- fold increase of SDCCAG28 mRNA in hepatoma cell line (Hep3B) upon 8 hours and 12 hours serum stimulation of quiescent cells, respectively (see Figure 106).

[152] Furthermore, the protein expression analyses show increase of SDCCAG28 protein signal in HCCs when compared to normal liver (Figure 105). The results support the functional significance of SDCCAG28 for disorders according to the invention, in particular for HCC.

[153] These data suggest that SDCCAG28 polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis, prevention and treatment of disorders according to the invention.

[154] In yet another preferred embodiment the nucleic acid according to the invention is the Peroxiredoxin 1 transcript variant 1, PRDX1 nucleic acid (SEQ ID 103) which has been disclosed before (Accession. No. NM_002574) encoding the PRDX1 polypeptide (Accession. No. NP_002565; SEQ ID 10), a member of the peroxiredoxin family of antioxidant enzymes (Prxs) that also control cytokine-induced peroxide levels which mediate signal transduction in mammalian cells. Prxs can be regulated by changes to phosphorylation, redox and possibly oligomerization states (Wood, Z.A., et al., 2003, Trends Biochem. Sci., 28 (1): 32- 40). Three transcript variants encoding the same protein have been identified for this gene. The PRDX1 has been shown to be up-regulated in human breast cancer (Noh DY et al., 2001, Anticancer Res., 21 (3B): 2085- 2090). However, neither PRDX1 nucleic acid nor the PRDX1 polypeptide had been recognized with respect to elevated levels in HCC.

[155] Expression of the mRNA encoding this polypeptide is elevated an average of 3.6-fold relative to non-diseased liver in 71% HCC cases profiled (Figure 1, Table 3A). Elevated expression of the encoding mRNA is also evident in other liver disorders (FNH, Cirrhosis) (Figure 18 and Tables 4A/5A).

[156] Independent verification analyses of expression levels of PRDX1 mRNA might be determined with gene specific oligonucleotide primers including, for example primer pairs specific to PRDX1 nucleic acid (Assay ID Catalogue Number: Hs00602020_m1) in the Assay-On-Demand (Applied Biosystems, USA) quantitative PCR method.

[157] These findings suggest that the PRDX1 polypeptide and/or a functional variant thereof and/or the encoding nucleic acid and/or a variant thereof can be utilized for the diagnosis, prevention and treatment of disorders according to the invention.

[158] In yet another preferred embodiment the nucleic acid according to the invention is the Transmembrane trafficking protein, TMP21 nucleic acid (SEQ ID 104) which has been disclosed before (Accession. No NM_006827) encoding the TMP21 polypeptide (Accession No. NP_006818, SEQ ID 11). Tmp21 is involved in biosynthetic transport from the endoplasmic reticulum to the Golgi complex (Blum,R., et al., 1996, J. Biol. Chem. 271, 17183- 17189).There are two known Tmp21 isoforms -I and –II, wherein hum-Tmp21-II is transcribed, but not translated (Horer J et al., 1999, DNA Seq., 10(2): 121-6). Recent data report that phorbol esters translocate beta2-chimaerin (member of "non-protein kinase C" (PKC) phorbol ester/diacylglycerol receptors family) to the perinuclear region and promote its association with Tmp21-I in a PKC-independent manner (Wang H and Kazanietz MG,J Biol Chem, 2002; 277(6): 4541- 4550). Thus, Tmp21-I might be serving as an anchoring protein that determines the intracellular localization of these novel phorbol ester receptors. The gene encoding both isoforms has not previously been reported to be expressed at elevated levels in disorders according to the invention, in particular in HCC.

[159] Expression of the mRNA encoding the TMP21 polypeptide is induced by an average of 8.5-fold relative to non-diseased liver in 26% of the HCC cases profiled (Figure 1, Table 3A). Similarly, elevated expression of the encoding mRNA is also evident in FNH but not in the cirrhotic livers (see Figure 19 and Tables 4A/5A).

[160] Furthermore, the expression of this HCC-deregulated mRNA is showing 2.6-fold and 3.5-fold increase by serum stimulation of quiescent hepatoma cells (HepG2) upon 8 hours and 12 hours, respectively (Figure 107).

[161] These results show that the differential upregulated expression of the TMP21 cDNA sequence is highly specific for disorders according to the invention. Therefore theTMP21 polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis, prevention and treatment of disorders according to the invention

[162] In yet another preferred embodiment the nucleic acid according to the invention is

the IQ motif containing GTPase-activating protein 2, IQGAP2 nucleic acid (SEQ ID 105) which has been disclosed before (Accession No. NM_006633) encoding the IQGAP2 polypeptide (Accession No. NP_006624, SEQ ID 12). This liver specific protein has been reported to harbor a potential actin binding domain and to interact with calmodulin and Rho family GTPases (Brill S et al., 1996, Mol Cell Biol.; 16(9): 4869-4878). The recent observations identify a physiologic scaffolding function for IQGAP2 representing a functional genomic unit in humans uniquely evolved to regulate thrombin-induced plateletcytoskeletal actin reorganization (Schmidt VA., 2003, Blood, 101(8): 3021-3028), but the gene encoding these isoforms has not previously been reported to be expressed at elevated levels in HCC.

[163] Expression of the mRNA encoding the IQGAP2 polypeptide is induced by an average of 4-fold relative to non-diseased liver in 71% of the HCC cases profiled (Figure 1, Table 3A). Similarly, elevated expression of the encoding mRNA is also evident in FNH but not in the cirrhotic livers (Figure 20 and Tables 4A/5A).

[164] The HCC induction of the IQGAP2 gene can then be verified by amplification of the sequence from the cDNA with primer pairs specific to IQGAP2 nucleic acid (Assay ID Catalogue Number: Hs00183606_m1) in the Assay-On-Demand (Applied Biosystems, USA) quantitative PCR method. These data suggest that the IQGAP2 polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis, prevention and treatment of disorders according to the invention.

[165] In yet another preferred embodiment the nucleic acid according to the invention is the member of RAS oncogene family, Rab2 nucleic acid (SEQ ID 106) which has been disclosed before (Accession No. NM_002865) encoding the Rab2 polypeptide (Accession No. NP_002865, SEQ ID 13). The small GTPase Rab2 is a resident of pre-Golgi intermediates and required for protein transport from the endoplasmic reticulum (ER) to the Golgi complex (Tisdale, E. J. et al., 1992, J. Cell Biol., 119: 749- 761). The Rab2 protein, like all small GTPases, contains conserved GTP-binding domains as well as hypervariable carboxyl-terminal and amino-terminal domains. It is suggested that the NH2 terminus of Rab2 is required for its function and for direct interaction with components of the transport machinery involved in the maturation of pre-Golgi intermediates. Rab2 interacts directly with atypical protein kinase C (aPKC) iota/ lambda and inhibits aPKC iota/lambda-dependent glyceraldehyde-3-phosphate dehydrogenase phosphorylation (Tisdale, E.J.2003, J Biol Chem.; 278(52):52524-30). Though overexpression in lymphoid and myeloid malignancies has been reported, neither Rab2 nucleic acid nor the Rab2 polypeptide has been recognized with respect to elevated levels in disorders according to the invention, preferably in HCC.

[166] Expression of the mRNA encoding this polypeptide is elevated an average of 5-fold relative to non-diseased liver in 71% of the HCC cases profiled (Figure 2, Table 3A).

Elevated expression of the encoding mRNA is also evident in FNH but not in cirrhosis (Figure 21 and Tables 4A/ 5A).

[167] Furthermore, the expression of this HCC-deregulated mRNA is 5.5-fold and almost 8-fold increased by serum stimulation of quiescent hepatoma cells (Hep3B) upon 8 hours and 12 hours, respectively (Figure 106).

[168] These findings suggest that the Rab2 polypeptide and/or the encoding nucleic acid can be utilized for the diagnosis, prevention and treatment of disorders according to the invention.

[169] In another preferred embodiment the nucleic according to the invention is the Clone 6 cDNA (OBCL6, SEQ ID 125), which is assembled by identification of overlapping sequences from the non-redundant GenBank sequence databases. The initial EST sequence upregulated in HCC relative to non-diseased liver identified with cDNA microarray analysis shows the highest similarity (almost 100% identical) to human genomic clone AL035420 (human DNA sequence from clone RP4-550H1 on chromosome 20q11.1-11.22 containing a high mobility group protein pseudogene). It may be that extending the length of this HCC-deregulated cDNA sequence will reveal that the corresponding RNA encodes a not yet described human protein. Another alternative is that the encoded polypeptide may result from one of the small open reading frames in this sequence. Even further, this RNA may be not translated into polypeptide but may have functional (e.g., regulatory) properties itself.

[170] Surprisingly the sequence from this mRNA is represented at much higher levels in HCC than in normal human liver. This mRNA is elevated an average of 6-fold or more relative to non-diseased liver in 68% of HCC samples profiled (Table 3B, Figure 3). Clone 6 is also elevated 8-fold or more relative to non-diseased liver in FNHs examined, but not in cirrhosis (Figure 40, Tables 4b/5B). Independent RT-PCR analyses of expression levels of might be determined with gene specific oligonucleotide primers. These results show that the strongly upregulated expression of the Clone 6 cDNA sequence is highly specific for disorders according to the invention, especially in HCC and FNH.

[171] Overexpression of the polypeptide and/or the encoding RNA therefore, may be useful for diagnosis of liver disorders. These results clearly demonstrate that the Clone 6 polypeptide and the nucleic acid (SEQ ID 125) encoding the polypeptide (SEQ ID 32) and a functional variant thereof can be utilized for diagnosis, prevention and treatment of disorders according to the invention, in particular for HCC and FNH.

[172] With regard to the treatment it is preferred to carry out the treatment such that the expression of the OBCL6 polypeptide and/or a functional variant thereof; or of the nucleic acid encoding the polypeptide and/or a functional variant thereof is reduced and/or inhibited, for example by administering antisense oligonucleotides or small in-

terfering RNA molecules that specifically interact with the nucleic acid defined in SEQ ID 125 potentially encoding the OBCL6 polypeptide and/or a functional variant thereof.

[173] The treatment may be carried out, for example, such that the activity of the Clone 6 polypeptide and/or a functional variant thereof are reduced and/or inhibited, for instance by administering an antibody directed against the OBCL6 polypeptide and/or a functional variant thereof, or an antibody fragment thereof which block the activity of the Clone 6 polypeptide and/or a functional variant thereof to a patient in need of such treatment. Compared to the state of the art, the OBCL6 polypeptide and/or a functional variant thereof; and/or OBCL6 nucleic acid surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis and/or improved, sustained and/or more effective treatment of the liver disorders and/or other epithelial cancer.

[174] Alternatively, the OBCL6 RNA may be not translated into a polypeptide but may have functional (e.g., regulatory) properties itself. The disease relevance of non-coding regulatory RNAs is now becoming apparent as evidenced, for example, by the role of the non-coding RNA "bantam" involved in cellular proliferation in the eukaryote Drosophila (Brennecke J, Hipfner DR, Stark A, Russell RB, Cohen SM. Cell (2003) Apr4; 113(1):25-36), and by microRNA-23 that interacts with the transcription factor HES-1 to hinder neuronal differentiation (Kawasaki, H. and Tiara, K. Nature, 2003, 423:838-842).

[175] For example, reduction of the level of Clone 6 RNA (knock-down) in proliferating human hepatoma cells with small interfering RNA (siRNA) oligonucleotides can support a functionally significant role for elevated expression of Clone 6 RNA in liver disorders, especially liver cancer.

[176] Further aspect of the invention represents an isolated polypeptide comprising a sequence according to the SEQ ID 32 or a functional variant thereof. Another preferred embodiment is a fusion protein, wherein the fusion protein contains the polypeptide according to the SEQ ID 32 or a functional variant thereof.

[177] Yet another preferred feature of the invention is an isolated nucleic acid according to the SEQ ID 125 or a variant thereof. Further preferred embodiment represents the nucleic acid according to the SEQ ID 125 or a variant thereof, wherein the nucleic acid is a single-stranded or double-stranded RNA.

[178] Still another aspect of the invention represents a nucleic acid according to the SEQ ID 125 or a variant thereof encoding the polypeptide according to the SEQ ID 32 or a functional variant thereof.

[179] Yet another feature of the invention is a vector, wherein the vector contains a nucleic acid selected from the group consisting of a nucleic acid according to the SEQ

ID 125 or a variant thereof encoding the polypeptide according to the SEQ ID 32 or a functional variant thereof. The vector is preferably selected from the group consisting of a knock-out gene construct, a plasmid, a shuttle vector, a phagemid, a cosmid, a viral vector, and an expression vector.

[180] Another aspect of the invention represents a cell, wherein the cell contains the nucleic acid according to the SEQ ID 125 or a variant thereof encoding the polypeptide according to the SEQ ID 32 or a functional variant thereof. In another preferred embodiment the cell is transformed with a vector containing a nucleic acid selected from the group consisting of a nucleic acid according to the SEQ ID 125 or a variant thereof encoding the polypeptide according to the SEQ ID 32 or a functional variant thereof. In still further embodiment of the invention the cell is a transgenic embryonic non-human stem cell.

[181] Yet another feature of the invention represents a transgenic non-human mammal, wherein the transgenic non-human mammal contains the nucleic acid according to the SEQ ID 125 or a variant thereof encoding the polypeptide according to the SEQ ID 32 or a functional variant thereof.

[182] Further aspect is an antibody or an antibody fragment thereof, wherein the antibody is directed against the polypeptide according to the SEQ ID 32 or a functional variant thereof, or against a nucleic acid coding for the polypeptide.

[183] The cDNA expression levels relative to a non-diseased liver (NL) reference sample of sequences according to the invention assessed in tissues from human liver disorders, including Hepatocellular Carcinoma (HCC), Focal Nodular Hyperplasia (FNH) and Cirrhosis (Cirrh.) samples are shown in Tables 3A to 3D, 4A to 4D and 5A to 5D, respectively (median of $\log_2$ values data between diseased and non-diseased samples obtained from competitive hybridisation to custom-made cDNA microarrays). Median represents 50^{th} percentile of values for each sequence (SEQ ID 94 to 186) per group (HCC, FNH and Cirrh). Number of the samples profiled and the calculated percentage of valid/detectable signals (% detected) are provided. (*) annotates duplicates of the HCCs, FNHs, and Cirrh. profiled.

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[196] **Tables 3A to 3D: Summary of c DNA microarray expression level ratios (HCC vs NL).**

Table 3A

Gene	Median $\log_2$	Median-fold induction	HCC microarray hybridizations (No)	Detected (%)
PI4K2	0.75	1.68	28	54
ZNF216	4.01	16.07	28	54
AKR1C1	2.78	6.86	56	79
dUT	2.80	6.96	28	46
PACE4	4.60	24.23	28	57
BIGH3	2.31	4.95	28	79
PRKAR1A	1.73	3.32	56	39
s.t. Ocia	1.29	2.45	56	32
SDCCAG28	1.64	3.12	28	71
PRDX1	1.86	3.63	56	71
TMP21	3.08	8.46	56	27
IQGAP2	2.00	3.99	28	71
Rab2	2.38	5.21	28	71
ARF1	3.12	8.71	28	54
HSPC1	2.19	4.55	56	23
TLR5	1.55	2.93	28	64
GAP-SH3	1.72	3.29	28	71
Crisp-3	1.92	3.77	28	57
TM4SF4	1.70	3.24	56	32
AQP9	1.17	2.25	84	36
LOC51716	0.85	1.80	112	72
Cystatin	3.28	9.70	28	46

Ki	2.55	5.85	28	68

[197]

[198]

Table 3B

Gene	Median $\log_2$	Median-fold induction	HCC microarray hybridizations (No)	Detected (%)
Porimin	3.00	7.97	56	9
PTPRZ1	1.94	3.84	84	13
Rab9 effector p40	3.49	11.26	28	39
RBap48	3.10	8.58	28	50
PABPC1	3.69	12.89	28	61
NF1/B2	0.72	1.65	56	57
RPL7	3.08	8.46	140	19
HNRPDL	1.78	3.44	140	26
OBCL6	2.59	6.02	28	32
SNRPG	2.39	5.26	56	23
KREV-1	1.51	2.85	28	61
DRB5	1.62	3.08	28	79
PKCI-1	0.62	1.54	28	82
IMPACT	4.03	16.37	28	36
BMI	3.52	11.48	56	16
G3BP	3.40	10.56	28	46
RHEB2	3.31	9.92	28	57
MARCKS	2.68	6.43	56	43
ALURBP	3.01	8.04	28	36
PPGB	2.70	6.49	28	79
GRB2	2.75	6.71	28	43
TRAP1	3.24	9.44	56	20
PDHB	3.05	8.25	28	46

[199]

Table 3C

Gene	Median $\log_2$	Median-fold induction	HCC microarray hybridizations (No)	Detected (%)
DAD-1	2.02	4.06	56	63
PSME2	2.61	6.11	28	32
QP-C	2.27	4.83	28	79
MTRPS33	2.63	6.20	56	25
ARF4	3.02	8.12	28	36
DDB1	2.23	4.70	28	32
GNG10	1.80	3.49	56	66
DP1	2.68	6.40	56	27
ATP1B1	2.35	5.11	56	39
SLC25A3	2.25	4.75	56	39
SNC6	1.86	3.63	28	61
OMG	2.17	4.51	28	36
PB1S	2.17	4.51	28	36
RPS21	1.75	3.35	112	62
MMP-2	1.80	3.48	28	39
YWHAZ	1.87	3.66	28	89
PPP3R1	1.83	3.56	56	46
CTNNA1	1.11	2.15	112	29
ADCYAP1	0.74	1.67	28	4
syntenin	1.93	3.82	28	79
topoisomerase IIb	2.25	4.76	28	18
UMP-CMPK	1.63	3.09	84	18
PSMD4	2.48	5.59	56	29
hu_BTF3	1.83	3.57	28	86
rhoA	1.68	3.21	28	68

[200]

Table 3D

Gene	Median log $_2$	Median-fold induction	HCC microarray hybridizations (No)	Detected (%)
LDH-B	1.58	2.99	56	63
TBXA2-R	1.64	3.12	56	38
hu_CAP	1.58	2.98	28	54
hu_PP2a-cat	1.49	2.82	196	6
SDHC	1.55	2.94	56	36
hu_GDP-di2	1.54	2.90	28	32
CCNI	1.70	3.26	28	64
Mac25	1.58	2.98	28	14
TBP	1.10	2.14	84	39
FDX1	1.79	3.46	28	36
NLVCF	1.34	2.53	56	32
GNG3	1.32	2.49	28	32
RCN2	1.88	3.67	56	25
hu_adk2	1.00	2.00	28	46
hu_Dcsa19	1.54	2.91	28	93
c/EBP	1.64	3.11	84	24
Rab GG	1.29	2.44	28	54
**c-syn	2.24	4.74	56	18
PPP1R15A	1.34	2.54	28	36
SCL5A6	3.70	13.00	28	36

[201]

[202] [(**) c-syn represents three alternative nucleotide transcripts with corresponding three protein products

[203]

[204] **Tables 4A to 4D: Summary of c DNA microarray expression level ratios (FNH**

vs NL).

Table 4A

Gene	Median log_2	Median-fold induction	FNH microarray hybridizations (No)	Detected (%)
PI4K2	1.97	3.91	5	80
ZNF216	2.86	7.25	5	40
AKR1C1	1.18	2.27	10	70
dUT	3.41	10.60	5	40
PACE4	3.65	12.57	5	60
BIGH3	2.02	4.06	5	80
PRKAR1A	1.71	3.28	10	40
s.t. Ocia	0.48	1.40	10	40
SDCCAG28	2.73	6.61	5	40
PRDX1	0.65	1.57	10	70
TMP21	3.68	12.81	10	20
IQGAP2	2.33	5.01	5	80
Rab2	2.57	5.95	5	60
ARF1	2.07	4.18	5	40
HSPC1	2.19	4.57	10	30
TLR5	1.95	3.86	5	60
GAP-SH3	2.86	7.24	5	60
Crisp-3	1.45	2.73	5	60
TM4SF4	2.07	4.19	10	50
AQP9	0.60	1.51	15	33
LOC51716	0.67	1.59	20	75
Cystatin	2.10	4.28	5	20
Ki	2.14	4.41	5	60

[205]

Table 4B

Gene	Median log_2	Median-fol	FNH	Detected (%)

		d induction	**microarray hybridizati ons (No)**	
Porimin	NA	NA	10	0
PTPRZ1	2.89	7.43	15	20
Rab9 effector p40	NA	NA	5	0
RBap48	3.54	11.67	5	40
PABPC1	1.81	3.50	5	40
NF1/B2	0.64	1.56	10	70
RPL7	3.67	12.69	25	12
HNRPDL	2.25	4.75	25	16
OBCL6	3.07	8.42	5	40
SNRPG	1.38	2.60	10	20
KREV-1	3.73	13.29	5	80
DRB5	0.82	1.77	5	80
PKCI-1	-0.03	0.98	5	80
IMPACT	NA	NA	5	0
BMI	2.97	7.82	10	10
G3BP	3.60	12.13	5	20
RHEB2	3.28	9.68	5	20
MARCKS	1.75	3.35	10	40
ALURBP	1.15	2.22	5	20
PPGB	2.35	5.10	5	80
GRB2	2.89	7.41	5	20
TRAP1	NA	NA	10	0
PDHB	3.79	13.79	5	60

[206]

Table 4C

Gene	Median log 2	Median-fold induction	FNH microarray hybridizations (No)	Detected (%)
DAD-1	2.01	4.02	10	60
PSME2	NA	NA	5	0
QP-C	1.15	2.21	5	80
MTRPS33	2.88	7.34	10	10
ARF4	3.78	13.76	5	80
DDB1	2.97	7.86	5	40
GNG10	2.87	7.32	10	70
DP1	2.58	5.97	10	20
ATP1B1	1.70	3.26	10	10
SLC25A3	2.95	7.74	10	30
SNC6	0.76	1.69	5	40
OMG	3.31	9.94	5	60
PB1S	1.39	2.62	5	20
RPS21	1.41	2.65	20	50
MMP-2	4.28	19.41	5	20
YWHAZ	1.00	2.00	5	80
PPP3R1	1.54	2.90	10	30
CTNNA1	2.08	4.24	20	40
ADCYAP1	NA	NA	5	0
syntenin	1.83	3.55	5	80
topoisomerase IIb	2.96	7.75	5	40
UMP-CMPK	3.02	8.11	15	27
PSMD4	1.34	2.53	10	10
hu_BTF3	1.01	2.01	5	80
rhoA	1.16	2.23	5	60

[207]

Table 4D

Gene	Median $\log_2$	Median-fold induction	FNH microarray hybridizations (No)	Detected (%)
LDH-B	1.58	2.99	10	80
TBXA2-R	1.64	3.12	10	40
hu_CAP	1.58	2.98	5	60
hu_PP2a-cat	1.49	2.82	35	11
SDHC	1.55	2.94	10	0
hu_GDP-di2	1.54	2.90	5	40
CCNI	1.70	3.26	5	80
Mac25	1.58	2.98	5	20
TBP	1.10	2.14	15	27
FDX1	1.79	3.46	5	40
NLVCF	1.34	2.53	10	10
GNG3	1.32	2.49	5	80
RCN2	1.88	3.67	10	10
hu_adk2	1.00	2.00	5	80
hu_Dcsa19	1.54	2.91	5	100
c/EBP	1.64	3.11	15	20
Rab GG	1.29	2.44	5	60
**c-syn	2.24	4.74	10	10
PPP1R15A	1.34	2.54	5	20
SCL5A6	3.70	13.00	5	20

[208]

[209] [(**) c-syn represents three alternative nucleotide transcripts with corresponding three protein products

[210]

[211] **Tables 5A to 5D: Summary of c DNA microarray expression level ratios (Cirrh. vs NL).**

Table 5A

Gene	Median log $_2$	Median-fold induction	Cirrh. microarray hybridizations (No)	Detected (%)
PI4K2	-0.23	0.85	8	88
ZNF216	NA	NA	8	0
AKR1C1	-0.72	0.61	16	50
dUT	0.40	1.32	8	13
PACE4	0.68	1.60	8	13
BIGH3	1.04	2.05	8	38
PRKAR1A	0.80	1.74	16	13
s.t. Ocia	0.12	1.09	16	6
SDCCAG28	0.35	1.28	8	25
PRDX1	1.38	2.60	16	44
TMP21	NA	NA	16	0
IQGAP2	0.51	1.42	8	50
Rab2	0.88	1.84	8	25
ARF1	1.24	2.36	8	25
HSPC1	-2.55	0.17	16	19
TLR5	1.08	2.12	8	38
GAP-SH3	1.60	3.04	8	25
Crisp-3	1.06	2.09	8	25
TM4SF4	1.23	2.35	16	25
AQP9	0.80	1.74	24	33
LOC51716	-0.56	0.68	32	66
Cystatin	3.15	8.88	8	25
Ki	1.01	2.01	8	25

[212]

Table 5B

Gene	Median log $_2$	Median-fold	Cirrh. microarray	Detected (%)

			induction		hybridizations (No)		
Porimin	1.13		2.19		16		6
PTPRZ1	1.21		2.32		24		8
Rab9 effector p40	NA		NA		8		0
RBap48	2.46		5.50		8		13
PABPC1	3.47		11.06		8		13
NF1/B2	1.33		2.51		16		44
RPL7	0.98		1.97		40		5
HNRPDL	-0.33		0.80		40		8
OBCL6	NA		NA		8		0
SNRPG	0.17		1.12		16		13
KREV-1	1.64		3.12		8		38
DRB5	0.32		1.25		8		63
PKCI-1	0.71		1.64		8		75
IMPACT	1.68		3.21		8		25
BMI	2.68		6.41		16		19
G3BP	1.60		3.03		8		13
RHEB2	1.04		2.06		8		13
MARCKS	1.77		3.40		16		25
ALURBP	-1.13		0.46		8		13
PPGB	1.66		3.16		8		50
GRB2	2.62		6.14		8		25
TRAP1	3.06		8.33		16		13
PDHB	1.43		2.69		8		38

[213]

[214]

Table 5C

Gene	Median log $_2$	Median-fold induction	Cirrh. microarray hybridizations (No)	Detected (%)
DAD-1	1.61	3.05	16	31
PSME2	0.98	1.97	8	38
QP-C	2.87	7.31	8	63
MTRPS33	NA	NA	16	0
ARF4	3.98	15.74	8	13
DDB1	4.11	17.30	8	13
GNG10	1.81	3.51	16	50
DP1	1.33	2.51	16	13
ATP1B1	2.33	5.02	16	19
SLC25A3	0.99	1.99	16	25
SNC6	1.11	2.16	8	50
OMG	1.95	3.87	8	25
PB1S	0.98	1.98	8	38
RPS21	1.16	2.24	32	47
MMP-2	1.00	2.00	8	38
YWHAZ	1.48	2.79	8	75
PPP3R1	1.40	2.64	16	31
CTNNA1	-0.46	0.73	32	22
ADCYAP1	NA	NA	8	0
syntenin	1.26	2.40	8	75
topoisomerase IIb	-0.10	0.93	8	13
UMP-CMPK	1.51	2.85	24	8
PSMD4	-1.63	0.32	16	13
hu_BTF3	1.73	3.33	8	63
rhoA	1.49	2.81	8	50

[215]

Table 5D

Gene	Median $\log_2$	Median-fold induction	Cirrh.microarray hybridizations (No)	Detected (%)
LDH-B	0.91	1.89	16	75
TBXA2-R	1.05	2.07	16	31
hu_CAP	1.63	3.10	8	25
hu_PP2a-cat	2.13	4.38	56	7
SDHC	NA	NA	16	0
hu_GDP-di2	1.44	2.71	8	50
CCNI	1.12	2.18	8	50
Mac25	1.09	2.13	8	25
TBP	0.76	1.69	24	4
FDX1	1.33	2.52	8	25
NLVCF	1.30	2.47	16	13
GNG3	-0.38	0.77	8	25
RCN2	1.35	2.56	16	6
hu_adk2	1.59	3.00	8	13
hu_Dcsa19	1.29	2.45	8	88
c/EBP	0.25	1.19	24	13
Rab GG	0.56	1.48	8	38
**c-syn	1.62	3.08	16	13
PPP1R15A	0.86	1.81	8	38
SCL5A6	3.95	15.45	8	25

[216]

[217] [(**) c-syn represents three alternative nucleotide transcripts with corresponding three protein products]

[218]

[219] The quantitative assessment of gene expression (SEQ IDs: 102; 99; 101; 106; 98; 96) by RT-PCR (Q-PCR) in Hepatocellular Carcinoma (HCC), Focal Nodular Hyperplasia (FNH) and Cirrhosis (Cirrh) samples is compared to expression pattern in

normal liver (NL), shown inTable 6 (median of $\log_2$ values). Median represents 50th percentile of values for each sequence per group (HCC, FNH and Cirrh). Number of the samples profiled (SDCCAG28, BIGH3, s.t.OCIA, Rab2 and PACE4) represent 18 HCC, 3 FNH/Cirrh./NL; and for AKR1C1 7 HCC and 4 NL. Percentage of valid/ detectable signals for SEQ IDs 102; 99; 101; 106; 98; 96 (% detected) is equal to 100%, with exception of PACE4 (*) for which 94.45% HCC cases are detected.

[220]

[221] **Table 6: Summary of differential gene expression levels (SEQ IDs: 102; 99; 101; 106; 98; 96) verified by RT-PCR**

Table 6

Tissue	SDCCAG 28	BIGH3	s.t.OCIA	Rab2	PACE4	AKR1C 1
HCC	0.75	1.54	1.6	2.25	0.5*	3.20
FNH	1.29	2.4	2.23	2.63	1.51	NA
Cirrh.	-0.28	0.51	0.83	1.27	1.89	NA
NL	-1.34	0	0.53	0.22	0	0.93

[222]

[223] The quantitative assessment of gene expression of TMF4SF4 and DAD-1 in Hepatocellular Carcinoma (HCC), Focal Nodular Hyperplasia (FNH) and Cirrhosis (Cirrh) samples is compared to expression pattern in normal liver (NL), shown in Tables 7A/7B respectively (median of $\log_2$ values). Median represents 50th percentile of values for each sequence (SEQ ID 112 and SEQ ID 140) per group (HCC, FNH and Cirrh). Median- fold induction is calculated according to following formula: "2^x" ("x" represents median of $\log_2$ values). Number of the samples profiled (TM4SF4 and DAD-1 genes) represent 18 HCC, 3 FNH/Cirrh./NL.

[224]

[225] **Table 7A/7B: Summary of differential gene expression levels (SEQ ID 112 and SEQ ID 140) verified by RT-PCR.**

[226] 6

Table 7A

TM4SF4	Median $\log_2$	Median-fold induction	Number of cases profiled
HCC	2.83	7.11	18
FNH	3.81	14.07	3
Cirrh.	2.66	6.30	3

NL	0	1	3

[227]

Table 7B

DAD-1	Median log 2	Median-fold induction	Number of cases profiled
HCC	0.62	1.54	18
FNH	1.21	2.31	3
Cirrh.	0.14	1.10	3
NL	0.20	1.15	3

[228]

[229] In another preferred embodiment of the invention the nucleic acid according to the invention can be used for the construction of antisense oligonucleotides (Zheng and Kemeny, 1995, Clin. Exp. Immunol., 100: 380-382) and/or ribozymes (Vaish et al., 1998, Nucleic Acids Res., 26: 5237-5242; Persidis, 1997, Nat. Biotechnol., 15: 921-922) and/or small interfering double stranded RNAs (Elbashir et al., 2001, Nature, 411: 494-498; Brummelkamp et al., 2002, Science, 296:550-553). In further preferred embodiments of the invention, the stability of the nucleic acid according to the invention can be decreased and/or the translation of the nucleic acid according to the invention inhibited by using RNA interference molecules (oligonucleotides). Thus, for example, the expression of the corresponding genes in cells can be decreased both *in vivo* and *in vitro*. Oligonucleotides can therefore be suitable as therapeutics. This strategy is also suitable, for example, for liver cells, in particular if the antisense oligonucleotides are complexed with liposomes. For use as a probe or as an "antisense" oligonucleotide, a single-stranded DNA or RNA is preferred. Small interfering RNA (siRNA) double stranded oligonucleotides can also be suitable as therapeutics. With this approach a short sequence or sequences of 15 to 22 nucleotides including sequence complementary to the sequence to be therapeutically targeted are exposed to the diseased tissue and serve to dramatically reduce or "knock down" the level of expression of the therapeutic target RNA sequence. siRNA therapeutic approaches in other diseases have been recently reported and are also applicable to liver disorders, liver cancers and other epithelial cancers (Filleur S. et al., Cancer Res., 2003; 63(14): 39-22).

[230] In a preferred embodiment a nucleic acid according to the invention has been prepared by recombinant methods, by screening a library or isolation from a sample obtained from a patient or a subject. In another preferred embodiment of the invention

the nucleic acid according to the invention has been prepared synthetically. Thus, the nucleic acid according to the invention can be synthesized, for example, chemically with the aid of the DNA sequences described in SEQ ID 94 to SEQ ID 186 and/or with the aid of the protein sequences described in SEQ ID 1 to SEQ ID 93 with reference to the genetic code, e.g. according to the phosphotriester method (see, for example, Uhlmann and Peyman, 1990, Chemical Reviews, 90:543-584).

[231] In another preferred embodiment, the invention relates to a nucleic acid according to the invention or a nucleic acid which is a non-functional mutant variant the nucleic acid or a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, which has been modified by attachment of chemical moieties to the nucleic acid to stabilize it against degradation, so that a high concentration of the nucleic acid is maintained in the cell over a long period (Beigelman et al., 1995, Nucleic Acids Res., 23: 3989-94; Dudycz, 1995, WO 95/11910; Macadam et al., 1998, WO 98/37240; Reese et al., 1997, WO 97/29116). Typically, such stabilization can be obtained by the introduction of one or more internucleotide phosphorus groups or by the introduction of one or more non-phosphorus internucleotides.

[232] Preferred suitable modified internucleotides are summarized in Uhlmann and Peymann (1990 Chem. Rev. 90, 544; see also Beigelman et al., 1995 Nucleic Acids Res., 23: 3989-94; Dudycz, 1995, WO 95/11910; Macadam et al., 1998, WO 98/37240; Reese et al., 1997, WO 97/29116).

[233] In a further embodiment the invention relates to a vector comprising a nucleic acid according to the invention and/or a variant thereof, or a nucleic acid which is a non-functional mutant variant of the nucleic acid, or a nucleic acid having a sequence complementary to one the aforementioned nucleic acids. Preferably the vector is a knock-out gene construct, a plasmid, a shuttle vector, a phagemid, a cosmid, a viral vector, an expression vector and/or a vector applicable in gene therapy. The preparation of such constructs is generally known to the person skilled in the art.

[234] An "expression vector" within the meaning of the present invention preferably comprises at least one promoter or enhancer, i.e. at least one regulatory element comprising at least one translation initiation signal, at least one of the nucleic acids according to the invention or a nucleic acid which is a non-functional mutant variant the nucleic acid or a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, one translation termination signal, a transcription termination signal, and a polyadenylation signal for the expression in eukaryotes.

[235] For the expression of the gene concerned, in general a double-stranded DNA is preferred, the DNA region coding for the polypeptide being particularly preferred. In the case of eukaryotes this region begins with the first start codon (ATG) lying in a Kozak sequence (Kozak, 1987, Nucleic. Acids Res., 15: 8125-48) up to the next stop

codon (TAG, TGA or TAA), which lies in the same reading frame to the ATG. In the case of prokaryotes this region begins with the first AUG (or GUG) after a Shine-Dalgarno sequence and ends with the next stop codon (TAA, TAG or TGA), which lies in the same reading frame to the ATG.

[236] Differentially expressed genes in HCC can contain liver or liver cancer gene-specific regulatory sequences. These non-transcribed sequences, found in the tissue- or disease-specific gene may be used to drive tissue- or disease-specific expression of included therapeutic and/or tumor cell-cytotoxic genes. These regulatory sequences may be used for liver cancer specific expression of a nucleic acid according to the invention or a nucleic acid which is a non-functional mutant variant the nucleic acid or a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids. The screening and construction of such regulatory sequences is generally known to the person skilled in the art.

[237] Suitable expression vectors can be prokaryotic or eukaryotic expression vectors. Examples of prokaryotic expression vectors are, for expression in *E. coli*, e.g. the vectors pGEM or pUC derivatives, examples of eukaryotic expression vectors are for expression in *Saccharomyces cerevisiae*, e.g. the vectors p426Met25 or p426GAL1 (Mumberg et al., 1994, Nucl. Acids Res., 22, 5767-5768), for expression in insect cells, e.g. *Baculovirus* vectors such as disclosed in EP-B1-0 127 839, and for expression in mammalian cells, e.g. the vectors Rc/CMV and Rc/RSV or SV40 vectors, which are all generally obtainable. Specific vectors for production of RNA interference following transfection, such as the pSUPER vector (Brummelkamp et al., 2002, Science, 296:550-553) are also included.

[238] In general, the expression vectors also contain promoters suitable for the respective cell, such as, for example, the trp promoter for expression in *E. coli* (see, for example, EP-B1-0 154 133), the MET 25, GAL 1 or ADH2 promoter for expression in yeast (Russel et al., 1983, J. Biol. Chem., 258, 2674-2682; Mumberg, supra), the Baculovirus polyhedrin promoter, for expression in insect cells (see, for example, EP-B1-0 127 839). For expression in mammalian cells, for example, suitable promoters are those which allow a constitutive, regulatable, tissue-specific, cell-cycle-specific or metabolically specific expression in eukaryotic cells. Regulatory elements according to the present invention preferably are promoters, activator sequences, enhancers, silencers and/or repressor sequences.

[239] Examples of suitable regulatory elements which make possible constitutive expression in eukaryotes preferably are promoters which are recognized by the RNA polymerase III or viral promoters, CMV enhancer, CMV promoter, SV40 promoter or LTR promoters, e.g. from MMTV (mouse mammary tumor virus; Lee et al., 1981, Nature, 214, 228-232) and further viral promoter and activator sequences, derived

from, for example, adeno- and adeno-like viruses, HBV, HCV, HSV, HPV, EBV, HTLV or HIV.

[240] Examples of regulatory elements which make possible regulated expression in eukaryotes are the tetracycline operator in combination with a corresponding repressor (Gossen et al., 1994, Curr. Opin. Biotechnol., 5:516-20).

[241] Translation initiation signals, translation termination signals, transcription termination signals, and polyadenylation signals are generally known to the person skilled in the art and can be readily obtained from commercial laboratory suppliers.

[242] Preferably, the expression of the genes relevant for liver disorders and/or epithelial cancer takes place under the control of tissue-specific promoters, for example, under the control of liver-specific promoters such as albumin, alpha fetoprotein, apolipoprotein AI, alpha-1 antitrypsin, and the complement C5 and C8A genes (Schrem et al., 2002, Pharmacol. Rev., 54 129-58; Pontoglio et al., 2001, J. Expt. Med., 194:1683-1689). The regulatory sequences associated with genes highly deregulated in HCC as described herein also provide a preferable method for specific gene expression in these disorders.

[243] Further examples of regulatory elements which make tissue-specific expression in eukaryotes possible are promoters or activator sequences from promoters or enhancers of those genes which code for proteins which are only expressed in certain cell types.

[244] Examples of regulatory elements which make possible metabolically specific expression in eukaryotes are promoters which are regulated by hypoxia, by oxidative stress, by glucose deficiency, by phosphate concentration or by heat shock.

[245] Examples of regulatory elements which make cell cycle-specific expression in eukaryotes possible are promoters of the following genes: cdc25A, cdc25B, cdc25C, cyclin A, cyclin E, cdc2, E2F-1 to E2F-5, B-myb or DHFR (Zwicker J. and Müller R., 1997, Trends Genet., 13:3-6). The use of cell cycle regulated promoters is particularly preferred in cases, in which expression of the polypeptides or nucleic acids according to the invention is to be restricted to proliferating cells.

[246] In order to make possible the introduction of nucleic acids as described above, or a nucleic acid which is a non-functional mutant variant of the nucleic acid and thus the expression of the polypeptide in a eukaryotic or prokaryotic cell by transfection, transformation or infection, the nucleic acid can be present as a plasmid, as part of a viral or non-viral vector. Suitable viral vectors here are particularly: baculoviruses, vaccinia viruses, adenoviruses, adeno-associated viruses, retroviruses and herpesviruses. Suitable non-viral vectors here are particularly: virosomes, liposomes, cationic lipids, or polylysine-conjugated DNA or naked DNA.

[247] Plasmids, shuttle vectors, phagemids, and cosmids suitable for use according to the invention are also known to the person skilled in the art and are generally obtainable

from commercial laboratory suppliers.

[248] Examples of vectors applicable in gene therapy are virus vectors, for example adenovirus vectors, retroviral vectors or vectors based on replicons of RNA viruses (Lindemann et al., 1997, Mol. Med. 3: 466-476; Springer et al., 1998, Mol. Cell. 2:549-558). Eukaryotic expression vectors are suitable in isolated form for gene therapy use, as naked DNA can penetrate, for example, into liver cells upon local application or via the blood supply.

[249] Compared to the state of the art, this fusion construct surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive diagnosis and/or improved, sustained and/or more effective treatment of the liver disorders, and/or other epithelial cancers.

[250] In another aspect the invention furthermore relates to a cell comprising a nucleic acid according to the invention and/or a variant thereof. Preferably the cell is transformed with a vector according to the invention. The cell preferably contains a nucleic acid wherein the nucleic acid is either a non-functional mutant variant of a nucleic acid according to the invention. In particular the cell contains a vector comprising a nucleic acid wherein the nucleic acid is a non-functional mutant variant of a nucleic acid according to the invention. Preferably the cell contains a nucleic acid having a sequence complementary to a nucleic acid according to the invention, or a variant thereof. Moreover the cell preferably contains a vector comprising a nucleic acid coding for an antibody according to the invention or a fragment of the antibody. The cell according to the invention may for example be a liver cell, comprising at least one of the aforementioned nucleic acids or a cell which is transformed using one of the above described vectors. Cells can be either prokaryotic or eukaryotic cells, heterologous or autologous cells. Examples of prokaryotic cells are *E. coli* and examples of eukaryotic cells include primary hepatocytes cells, hepatocytes cell lines such as HepG2 and Hep3B cells, yeast cells, for example *Saccharomyces cerevisiae* or insect cells.

[251] Compared to the state of the art, the cell according to the invention surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive diagnosis and/or improved, sustained and/or more effective treatment of the liver disorders and/or other epithelial cancers.

[252] In a preferred embodiment of the invention the cell is a transgenic embryonic non-human stem cell which comprises at least one nucleic acid according to the invention, at least one vector, at least one knock-out gene construct and/or at least one expression vector as described above.

[253] Processes for the transformation of cells and/or stem cells are well known to a person skilled in the art and include, for example, electroporation or microinjection.

[254] In another aspect the invention relates to the provision of a transgenic non-human mammal comprising a compound selected from the group consisting of a nucleic acid according to the invention and/or a variant thereof, a nucleic acid which is a non-functional mutant variant the nucleic acid, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, one of the aforementioned nucleic acids in the form of a vector, of a knock-down or knock-out gene construct, and of an expression vector.

[255] Transgenic animals in general show a tissue-specifically increased expression of the nucleic acids and/or polypeptides and can be used for the analysis of liver disorders and/or epithelial cancers, such as for example HCC, and for development and evaluation of therapeutic strategies for such disorders. Transgenic animals may further be employed in the production of polypeptides according to the invention. The polypeptide produced by the animal may for example be enriched in a body fluid of the animal. The polypeptides according to the invention may for example be isolatable from a body fluid such as the milk.

[256] Compared to the state of the art, this transgenic non-human mammal surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive analysis and/or diagnosis of liver disorders and/or other epithelial cancers.

[257] Processes for the preparation of transgenic animals, in particular of transgenic mice, are likewise known to the person skilled in the art from e.g., US 5,625,122; US 5,698,765; US 5,583,278 and US 5,750,825 and include transgenic animals which can be produced, for example, by means of direct injection of expression vectors according to the invention into embryos or spermatocytes or by injection of the expression vectors into the pronucleus of the fertilized ovum or by means of the transfection of expression vectors into embryonic stem cells or by nuclear transfer into appropriate recipient cells (Polites and Pinkert, DNA Microinjection and Transgenic Animal Production, page 15 to 68 in Pinkert, 1994, Transgenic animal technology: a laboratory handbook, Academic Press, London, UK; Houdebine, 1997, Harwood Academic Publishers, Amsterdam, The Netherlands; Doetschman, Gene Transfer in Embryonic Stem Cells, page 115 to 146 in Pinkert, 1994, supra; Wood, Retrovirus-Mediated Gene Transfer, page 147 to 176 in Pinkert, 1994, supra; Monastersky, Gene Transfer Technology; Alternative Techniques and Applications, page 177 to 220 in Pinkert, 1994, supra).

[258] If the above described nucleic acids are integrated into so-called "targeting vectors" or "knock-out" gene constructs (Pinkert, 1994, supra), it is possible after transfection of embryonic stem cells and homologous recombination, for example, to generate knock-out mice which, in general, as heterozygous mice, show decreased expression of the nucleic acid, while homozygous mice no longer exhibit expression of the nucleic acid.

The animals thus produced can also be used for the analysis of liver disorders, such as for example HCC, and/or epithelial cancers.

[259] Knock-out gene constructs are known to the person skilled in the art, for example, from the US patents 5,625,122; US 5,698,765; US 5,583,278 and US 5,750,825.

[260] In a further aspect the invention relates to an antibody or a fragment, wherein the antibody or antibody fragment is directed against a polypeptide according to the invention, a functional variant thereof or against a nucleic acid coding for the polypeptide, or a variant thereof.

[261] Compared to the state of the art, these antibody or a fragment thereof surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis and/or improved, sustained and/or more effective treatment of the liver disorders and/or other epithelial cancers.

[262] The term "antibody" or "antibody fragment" is understood according to the present invention as also meaning antibodies or antigen-binding parts thereof prepared by genetic engineering and optionally modified, such as, for example, chimeric antibodies, humanized antibodies, multifunctional antibodies, bi- or oligospecific antibodies, single-stranded antibodies, F(ab) or $F(ab)_2$ fragments (see, for example, EP-B1-0 368 684, US 4,816,567; WO 98/24884). The antibodies according to the invention can for example be used for diagnosis, prevention and/or treatment of disorders according to the invention such as liver disorders, for example HCC, and/or epithelial cancers.

[263] The invention further relates to a method for producing an antibody or antibody fragment, preferably a polyclonal or monoclonal antibody, specific for the polypeptides or functional variants thereof encoded by the nucleic acids according to the invention, or variants thereof for example for the diagnosis and/or prevention and/or treatment of disorders according to the invention. The process is carried out according to methods generally known to the person skilled in the art by immunizing a mammal, for example a rabbit, with a nucleic acid according to the invention or their variants thereof, or with a polypeptide according to the invention or parts thereof or functional variants thereof, having at least 6 amino acid length, preferably having at least 8 amino acid length, in particular having at least 12 amino acid length, if appropriate in the presence of, for example, Freund's adjuvant and/or aluminum hydroxide gels (see, for example, Harlow and Lane, 1998, Using Antibodies: A Laboratory Manual, Cold Spring Harbor Press, New York, USA, Chapter 5, pp. 53-135). The polyclonal antibodies formed in the animal as a result of an immunological reaction can then be easily isolated from the blood according to generally known methods and purified, for example, by means of column chromatography. Monoclonal antibodies can be produced, for example, according to the known method

of Winter & Milstein (Winter and Milstein, 1991, Nature, 349:293-299).

[264] The present invention further relates to an antibody or antibody fragments directed against a polypeptide described above and reacts specifically with the polypeptides described above, where the above-mentioned parts of the polypeptide are either immunogenic themselves or can be rendered immunogenic by coupling to suitable carriers, such as, for example, bovine serum albumin or keyhole limpet hemocyanin to increase in their immunogenicity. This antibody is either polyclonal or monoclonal; preferably it is a monoclonal antibody.

[265] Still further, the present invention relates to the generation and/or production of an antibody or antibody fragment specific for the polypeptide according to the invention from a recombinant antibody expression library, such as for example described by Knappik et al. (2000, J. Molec. Biol., 296:57-86).

[266] In another embodiment of the invention, it is provided an array, wherein the array contains at least two compounds selected from the group consisting of a polypeptide according to the invention, a functional variant thereof, a nucleic acid encoding the polypeptide, a non-functional mutant variant nucleic acid and an antibody or an antibody fragment directed against the polypeptide. Alternatively, the array may contain at least one component according to the invention in combination with previously described components implicated in neoplastic or metabolic liver disorders or epithelial cancers.

[267] Within the meaning of the invention the term "array" refers to a solid-phase or gel-like carrier upon which at least two compounds are attached or bound in one-, two- or three-dimensional arrangement. Such arrays are generally known to the person skilled in the art and are typically generated on glass microscope slides, specially coated glass slides such as polycation-, nitrocellulose- or biotin- coated slides, cover slips, and membranes such as for example membranes based on nitrocellulose or nylon.

[268] The aforementioned arrays include bound polypeptides according to the invention or functional variants thereof or nucleic acids coding for the polypeptides, or variants thereof, fusion proteins according to the invention or antibodies or antibody fragments directed against polypeptides according to the invention or functional variants thereof or cells expressing polypeptides according to the invention or functional variants thereof or at least two cells expressing at least one nucleic acid according to the invention, or variants thereof. Nucleic acids coding for these, or variants thereof can also be part of an array. Such arrays can be employed for analysis and/or diagnosis of liver disorders, preferably of HCC, and/or epithelial cancer.

[269] The invention further relates to a method of producing arrays according to the invention, wherein at least two compounds according to the invention are bound to a carrier material.

[270] Methods of producing such arrays, for example based on solid-phase chemistry and photo-labile protective groups are generally known (US 5,744,305). Such arrays can also brought into contact with substances or a substance libraries and tested for interaction, for example for binding or change of conformation.

[271] The invention further relates to a process for preparing an array immobilized on a support material for analysis and/or diagnosis of disorders according to the invention such as a liver disorder, preferably of HCC, in which at least two nucleic acids, at least two polypeptides or at least two antibodies or antibody fragments, and/or at least two cells, or at least one of the aforementioned components in combination with other components relevant to neoplastic and metabolic liver disorders or epithelial cancers, as described above, is used for preparation. The arrays produced by such process can be employed for the diagnosis of disorders according to the invention.

[272] In another aspect the invention relates to a diagnostic comprising at least one compound selected from the group consisting of a polypeptide according to the SEQ ID 1 to SEQ ID 93 or functional variants thereof, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, and an antibody or an antibody fragment directed against one of the aforementioned polypeptides, combined or together with suitable additives or auxiliaries.

[273] In a preferred embodiment the invention relates to a diagnostic comprising a polypeptide according to the SEQ ID 1 or a functional variant thereof, a nucleic acid encoding the aforementioned polypeptide, a variant of the aforementioned nucleic acid, and an antibody or an antibody fragment directed against the aforementioned polypeptide, combined or together with suitable additives or auxiliaries.

[274] In a further aspect the invention relates to a diagnostic comprising at least one compound selected from the group consisting of a nucleic acid according to the SEQ ID 94 to SEQ ID 186 or variants thereof, combined with suitable additives or auxiliaries.

[275] In a preferred embodiment the invention relates to a diagnostic comprising a nucleic acid according to the SEQ ID 94 or a variant thereof, combined with suitable additives or auxiliaries

[276] Compared to the state of the art, this diagnostic surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive diagnosis of liver disorders and/or other epithelial cancers.

[277] Within the meaning of the invention "suitable additives" or "auxiliaries" are generally known to the person skilled in the art and comprise, for example, physiological saline solution, demineralized water, gelatin or glycerol-based protein stabilizing reagents. Alternatively, the nucleic acid or polypeptide according to the invention may be lyophilized for stabilization.

[278] In another examplea diagnostic kit based on the nucleic acid sequences according to the invention could be generated. Such a kit may be designed specifically to detect cells altered as a result of the described disorders resident in the circulatory system and thereby detectable in serum from test patients. Additional examples of diagnostic kits includes enzyme linked immunosorbent assays (ELISA), radioimmunoassays (RIA), and detection of an immune reaction or specific antibodies to the polypeptides according to the invention including detection of specific responding immune cells.

[279] In a preferred embodiment the diagnostic according to the invention contains a probe, preferentially a DNA probe.

[280] For example, it is possible according to the present invention to prepare a diagnostic based on the polymerase chain reaction (PCR). Under defined conditions, preferably using primers specific for a nucleic acid according to the invention as a DNA probe PCRs specific for the nucleic acid sequences of the invention will be utilized to monitor both the presence, and especially the amount, of specific nucleic acids according to the invention in a sample isolated from a patient obtained for diagnostic or therapeutic purposes. This opens up a further possibility of obtaining the described nucleic acids, for example by isolation from a suitable gene or cDNA library, for example from a liver disorder-specific or liver specific gene bank, with the aid of a suitable probe (see, for example, J. Sambrook et al., 1989, Molecular Cloning. A Laboratory Manual 2nd edn. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY Chapter 8 pages 8.1 to 8.81, Chapter 9 pages 9.47 to 9.58 and Chapter 10 pages 10.1 to 10.67).

[281] Suitable probes are, for example, DNA or RNA fragments having a length of about 50-1000 nucleotides, preferably having a length of about 10 to about 100 nucleotides, preferably about 100 to about 200 nucleotides, in particular having a length of about 200-500 nucleotides, whose sequence can be derived from the polypeptides according to SEQ ID 1 to SEQ ID 93, and functional variants thereof, and nucleic acids coding for the polypeptides, preferably according to SEQ ID 94 to SEQ ID 186, and variants thereof.

[282] Alternatively, it is preferably possible with the aid of the derived nucleic acid sequences to synthesize oligonucleotides that are suitable as primers for a polymerase chain reaction. Using this, the nucleic acid described above or parts of this can be amplified and isolated from cDNA, for example HCC-specific cDNA. Suitable primers are, for example, DNA fragments having a length of about 10 to 100 nucleotides, preferably having a length of about 15 to 50 nucleotides, in particular having a length of 17 to 30 nucleotides, whose sequence can be derived from the polypeptides according to SEQ ID 1 to SEQ ID 93 from the nucleic acids according to SEQ ID 94 to SEQ ID 186. The design and synthesis of such primers is generally known to the

person skilled in the art. The primers may additionally contain restriction sites, e.g. suitable for integration of the amplified sequence into vectors, or other adapters or overhang sequences, e.g. having a marker molecule such as a fluorescent marker attached, generally known to the skilled worker.

[283] In another aspect of the invention it is provided a method of diagnosis of a disorder according to the invention, wherein at least one compound selected from the group consisting of a polypeptide according to the sequence of SEQ ID 1 to SEQ ID 93, functional variants thereof, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, and an antibody directed against one of the aforementioned polypeptides or antibody fragment thereof, is identified in the sample of a patient and compared with at least one compound of a reference library or of a reference sample.

[284] In a preferred embodiment of the method the disorder of the liver is a disorder selected from the group consisting of cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's disease, haemochromatosis, hepatocellular carcinoma, benign liver neoplasms, and focal nodular hyperplasia.

[285] In a preferred embodiment of the method the epithelial cancer is an adenocarcinoma of any organ other than liver, preferably of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[286] Compared to the state of the art, this diagnostic surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive diagnosis of the liver disorders and/or other epithelial cancers.

[287] Preferably the sample is isolated from a patient by non-invasive methods as described above.

[288] For example, serum detection of specific deregulated gene proteins via ELISA assay is one application, alternatively one or a panel of antibodies to deregulated gene products may be used, from which a diagnostic score is deduced based on the combinations of, and the expression levels of gene products expressed in the diseased tissue or in serum from diseased individuals.

[289] A preferred diagnostic according to the invention contains the described polypeptide or the immunogenic parts thereof described in greater detail above. The polypeptide or the parts thereof, which are preferably bound to a solid phase, e.g. of nitrocellulose or nylon, can be brought into contact *in vitro*, for example, with the body fluid to be investigated, e.g. blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, in order thus to be able to react, for example, with autoimmune antibodies present in e.g. the blood of the patient. The antibody-peptide complex can then be detected, for example, with the aid of labeled antihuman IgG antibodies. The labeling involves, for example, an enzyme, such as peroxidase,

which catalyses a color or chemiluminescent reaction. The presence and the amount of autoimmune antibody present can thus be detected easily and rapidly by means of the color.

[290] In addition the diagnostic may be directed to detecting an endogenous antibody or fragment thereof present in the sample isolated from a patient which antibody or fragment thereof is directed against a polypeptide according to the invention. Detection of such autoimmune antibodies may be accomplished by methods generally known to the skilled artisan, e.g. by immunoaffinity assays using polypeptides according to the invention or functional variants thereof or parts thereof as a probe. Preferably the presence of such autoimmune antibodies is indicative of the patient suffering from a disorder according to the invention.

[291] A further diagnostic, that is subject matter of the present invention, contains the antibodies according to the invention themselves. With the aid of these antibodies, it is possible, for example, to easily and rapidly investigate a tissue sample as to whether the concerned polypeptide according to the invention is present in an increased amount in order to thereby obtain an indication of possible disease including liver disorders, for example HCC. In this case, the antibodies according to the invention are preferably labeled directly, or more commonly for example these are detected with a specific secondary antibody indirectly, such as with an enzyme or fluorescent molecule, as already described above. The specific antibody-peptide complex can thereby be detected easily, and rapidly, e.g., by means of an enzymatic color reaction.

[292] In still another aspect of the invention it is provided a method for identifying at least one nucleic acid according to the SEQ ID 94 to SEQ ID 186, or a variant thereof differentially expressed in a sample isolated from a patient relative to a reference library or a reference sample comprising the following steps: (a) detecting the expression of at least one nucleic acid according to the SEQ ID 94 to SEQ ID 186, or a variant thereof in a sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of the same nucleic acid(s) in a reference library or in a reference sample, (c) identifying said nucleic acid(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample.

[293] Compared to the state of the art the method surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive identification of differentially expressed nucleic acids according to the invention that provides a useful basis for diagnosing a disorder according to the invention.

[294] Preferably at least 2, at least 3, at least 4 at least 5, at least 6, or at least 7 nucleic acids are identified.

[295] In another preferred embodiment of the method said nucleic acid(s) is (are) detected

by PCR based detection or by a hybridization assay.

[296] In another preferred embodiment of the method the expression of said nucleic acid is compared by a method selected from the group consisting of solid-phase based screening methods, hybridization, subtractive hybridization, differential display, and RNase protection assay.

[297] In a further preferred embodiment of the method the sample isolated from the patient is selected from the group consisting of liver tissue, a liver cell, tissue from another organ subject to cancerous transformation, a cell from this organ, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[298] Preferably the reference sample is isolated from a source selected from a non-diseased sample of the same patient or a non-diseased sample from another subject. The selection of appropriate reference samples is generally known to the person skilled in the art. In particular the reference sample may be selected from the group consisting of liver tissue, a liver cell, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[299] In another preferred embodiment of the method, the reference library is an expression library or a data base comprising clones or data on non-diseased expression of at least one nucleic acid according to the invention in samples that preferably may be selected from the group consisting of liver tissue, a liver cell, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[300] In another aspect of the invention it is provided a method of diagnosing a liver disorder, or an epithelial cancer comprising the following steps: (a) detecting the expression of at least one nucleic acid according to the SEQ ID 94 to SEQ ID 186, or a variant thereof in a sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of the same nucleic acid(s) in a reference library or in a reference sample, (c) identifying said nucleic acid which is differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample, and (d) matching said nucleic acid(s) identified in step (c) with said nucleic acid(s) differentially expressed in a pathologic reference sample or pathologic reference library, wherein the matched nucleic acid(s) is (are) indicative of the patient suffering from a liver disorder or an epithelial cancer.

[301] Compared to the state of the art, this method of diagnosing surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive diagnosis of the liver disorders and/or other epithelial cancers.

[302] In another preferred embodiment of the method of diagnosis, the pathologic reference sample is isolated from a diseased sample from another patient. The latter patient having been diagnosed as suffering from the disorder according to the invention

which is to be diagnosed. The selection of appropriate pathologic reference samples is generally known to the person skilled in the art. In particular the pathologic reference sample may be selected from the group consisting of liver tissue, a liver cell, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[303] In another preferred embodiment of the method of diagnosis, the pathologic reference library is a data base comprising data on differential expression of the at least one nucleic acid according to the invention in samples isolated from at least one patient, excluding the patient under diagnosis, suffering from the disorder according to the invention to be diagnosed in the inventive method relative to control expression in a reference sample or reference library. The pathologic reference library preferably also relates to a differential expression library comprising nucleic acids according to the invention which are differentially expressed in samples isolated from at least one patient, excluding the patient under diagnosis, suffering from the disorder according to the invention to be diagnosed in the inventive method relative to control expression in a reference sample or reference library. The selection of an appropriate pathologic reference library is generally known to the person skilled in the art.

[304] Preferably the liver disorder is a disorder selected from the group consisting of cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's Disease, haemochromatosis, hepatocellular carcinoma, benign liver neoplasms, and focal nodular hyperplasia. In particular the epithelial cancer is an adenocarcinoma of any organ other than liver, preferably of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[305] Within the meaning of the invention the term "detecting a nucleic acid" refers to a method that preferably uncovers, visualizes, separates or allows recognition of the nucleic acid according to the invention from the background of the other components present in the sample. Such methods are generally known to the person skilled in the art and include in situ hybridization, PCR amplification, gel electrophoresis, northern blots, solid phase array (gene chips) based methods, nuclease protection methods (as described and referenced in Alberts, et al. 2002, The Molecular Biology of the Cell, 4^{th} ed. Garland, New York, USA).

[306] Within the meaning of the invention the term "comparing the expression of said nucleic acid(s) detected in step (a) with the expression of the same nucleic acid(s) in a reference library or in a reference sample" refers to a comparison of the expression of the two groups of said nucleic acid(s) on a quantitative or qualitative level by means of an experimental procedure such as differential display, subtractive hybridization, RNAse protection assay, or especially DNA chip hybridization. Moreover a comparison of experimental data on said nucleic acid(s) detected in step (a) with the

expression of the same nucleic acid(s) in a reference library as defined above is also included herein.

[307] The term "identifying said nucleic acid(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample" within the meaning of the present invention is understood to mean selecting said nucleic acid(s) which is (are) differentially expressed compared to the reference library or the reference samples which fulfills the following criteria: the level of differential expression of the detected said nucleic acid(s) compared to the reference library or the reference samples is greater than about 2 fold, preferably greater than about 5 fold, more preferred greater than about 10 fold upregulated.

[308] The term "matching said nucleic acid(s) identified in step (c) with said nucleic acid(s) differentially expressed in a pathologic reference sample or pathologic reference library " within the meaning of the invention is understood to mean that said nucleic acid(s) identified in step (c) is (are) compared with said nucleic acid(s) differentially expressed in a pathologic reference sample or pathologic reference library. Then said nucleic acid(s) identified in step (c) that is (are) also differentially expressed in the pathologic reference sample or pathologic reference library is (are) matched, i.e. said identical pair is identified and allocated. Since the differential expression of said nucleic acid(s) in the pathologic reference sample or pathologic reference library is (are) indicative of a disorder according to the invention, such correspondence with the differential expression in the sample then indicates that the patient suffers from that disorder.

[309] Preferably the sample is isolated from a patient by non-invasive or preferably minimally invasive methods such as described above, including venupuncture.

[310] The methods of diagnosing according to the invention allows early detection of a liver disorder and/or an epithelial cancer, and/or non-invasive diagnosis of the disorder, based on an essentially concordant expression pattern of the nucleic acids according to the invention detected in the samples isolated from an animal and/or a human patient suffering from a liver disorder and/or an epithelial cancer relative to a reference sample or relative to a reference library. The method has the additional advantage that it also provides additional and novel diagnostic parameters to characterize different subtypes of liver disorders, such as for example subtypes of HCC.

[311] The term "essentially concordant expression pattern" of the nucleic acids according to the invention refers to a pattern of expression that is essentially reproducible from patient to patient or subject to subject, provided that the patients or subjects compared are in the same or comparable pathological condition or healthy condition, respectively.

[312] In still another aspect of the invention it is provided a method for identifying at least one polypeptide according to the SEQ ID 1 to SEQ ID 93, or a functional variant thereof differentially expressed in a sample isolated from a patient relative to a reference library or a reference sample comprising the following steps: (a) detecting the expression of at least one polypeptide according to the SEQ ID 1 to SEQ ID 93, or a functional variant thereof in a sample isolated from a patient, (b) comparing the expression of said polypeptide(s) detected in step (a) with the expression of said polypeptide(s) in a reference library or in a reference sample, (c) identifying said polypeptide(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample.

[313] Compared to the state of the art, this method surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive identification of differentially expressed polypeptides according to the invention that provides a useful basis for diagnosing a disorder according to the invention.

[314] Preferably at least 2, at least 3, at least 4, at least 5, at least 6, or at least 7 polypeptides are identified.

[315] Preferably the sample is isolated from a patient by non-invasive or minimally invasive methods such as described above, including venupuncture.

[316] In another embodiment of the method the sample is a sample as defined further above. Preferably the reference sample is a reference sample as defined above.

[317] In another preferred embodiment of the method, the reference library is an expression library or a data base comprising clones or data on non-diseased expression of the at least one polypeptide according to the invention in samples that preferably may be selected from the group consisting of liver tissue, a liver cell, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, or feces. Such databases are generated as a result of the cDNA microarray expression analysis according to the invention and are known to persons skilled in the art. Further reference libraries useable according to the invention have been described above.

[318] In another aspect of the invention it is provided a method of diagnosing a liver disorder or an epithelial cancer comprising the following steps: (a) detecting the expression of at least one polypeptide according to the SEQ ID 1 to SEQ ID 93, or a functional variant thereof in a sample isolated from a patient, (b) comparing the expression of said polypeptide(s) detected in step (a) with the expression of said polypeptide(s) in a reference library or in a reference sample, (c) identifying said polypeptide(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample, and (d) matching said polypeptide(s) identified in step (c) with said polypeptide(s) differentially expressed in a pathologic reference sample orpathologic reference library, wherein the

matched polypeptide(s) is (are) indicative of the patient suffering from a liver disorder or an epithelial cancer.

[319] Compared to the state of the art, this method of diagnosing surprisingly allows improved, more sensitive, earlier, faster, and/or non-invasive diagnosis of the liver disorders and/or other epithelial cancers.

[320] Preferably at least 2, at least 3, at least 4, at least 5, at least 6, or at least 7 polypeptides are identified.

[321] Within the meaning of the invention the term "detecting a polypeptide" refers to a method that preferably uncovers, visualizes, separates and/or allows recognition of the polypeptide according to the invention from the background of the other components present in the sample. Such methods are generally known to the person skilled in the art and includes gel electrophoresis, chromatographic techniques, immunoblot analysis, immunohistochemistry, enzyme based immunoassay, mass spectroscopy, high pressure liquid chromatography, surface plasmon resonance, and/or antibody and protein arrays as described above (Ausubel, F.A. et al., eds., 1990, Current Protocols in Molecular Biology. Greene Publishing and Wiley-Interscience, New York, USA, Chapter 10; Myszka and Rich 2000, Pharm. Sci. Technol. Today 3:310-317). Preferably proteins and polypeptides are prepared from the sample by disruption of the cells with physical sheering or ultrasonic means, for example. Protein is denatured and stabilized with reducing agent treatment and heating and the protein is size fractionated on electrophoretic polyacrylamide gels.

[322] Within the meaning of the invention the term "comparing the expression of said polypeptide(s) detected in step (a) with the expression of the same polypeptide(s) in a reference library or in a reference sample " refers to a comparison of the expression of the two groups of polypeptide(s) on a quantitative and/or qualitative level by means of an experimental procedure such as two dimensional gel electrophoresis, chromatographic separation techniques, immunoblot analysis, surface plasmon resonance, immunohistochemistry, and enzyme based immunoassay. In two dimensional gel electrophoresis, all peptides are first resolved according to isoelectric point in the first electrophoretic dimension and then by size according to methods well known to persons experienced in the art. Moreover a comparison of experimental data on the at least one polypeptide detected in step 1 with the expression of the polypeptide in a reference library as defined above is also included herein.

[323] The term "Identifying said polypeptide(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample" within the meaning of the present invention is understood to mean selecting said polypeptide(s) which is (are) differentially expressed compared to the reference library or the reference samples which fulfills the following criteria: the level of dif-

ferential expression of the detected polypeptide(s) compared to the reference library or the reference samples is greater than about 2 fold, preferably greater than about 5 fold, more preferred greater than about 10 fold upregulated.

[324] The term "matching said polypeptide(s) identified in step (c) with said polypeptide(s) differentially expressed in a pathologic reference sample or pathologic reference library " within the meaning of the invention is understood to mean that said polypeptide(s) identified in step (c) is compared with said polypeptide(s) differentially expressed in a pathologic reference sample or pathologic reference library. Then said polypeptide(s) identified in step (c) that is (are) also differentially expressed in the pathologic reference sample or pathologic reference library is (are) matched, i.e. said identical pair(s) is (are) identified and allocated. Since the differential expression of said polypeptide(s) in the pathologic reference sample or pathologic reference library is (are) indicative of a disorder according to the invention, such correspondence with the differential expression in the sample then indicates that the patient suffers from that disorder.

[325] Preferably the sample is isolated from a patient by non-invasive or minimally invasive methods such as described above, including venupuncture.

[326] In another embodiment of the method the sample is a sample as defined further above. Preferably the reference sample is a reference sample as defined above.

[327] In another preferred embodiment of the method of diagnosis, the reference library is an expression library or a dataset comprising clones or data on non-diseased expression of the at least one polypeptide according to the invention in samples that preferably may be selected from the group consisting of liver tissue, a liver cell, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[328] An example of a data base according to the invention and further experimental reference libraries useable according to the invention have been described above.

[329] In another preferred embodiment of the method of diagnosis, the pathologic reference sample is a pathologic reference sample as has been defined above.

[330] In another preferred embodiment of the method of diagnosis, the pathologic reference library is a data base comprising data on differential expression of said polypeptide(s) according to the invention in samples isolated from at least one patient, excluding the patient under diagnosis, suffering from the disorder according to the invention to be diagnosed in the inventive method relative to control expression in a reference sample or reference library. The pathologic reference library also relates to a differential expression library comprising polypeptides according to the invention which are differentially expressed in samples isolated from at least one patient, excluding the patient under diagnosis, suffering from the disorder according to the

invention to be diagnosed in the inventive method relative to control expression in a reference sample or reference library. The selection of an appropriate pathologic reference library is generally known to the person skilled in the art.

[331] Preferably the liver disorder is a disorder selected from the group consisting of cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's Disease, haemochromatosis, hepatocellular carcinoma, benign liver neoplasms, and focal nodular hyperplasia. In particular the epithelial cancer is an adenocarcinoma of any organ other than liver, preferably of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[332] The methods of diagnosing according to the invention allows early detection of a liver disorder and/or epithelial cancer, and/or non-invasive diagnosis of the disorder, based on an essentially concordant expression pattern of the polypeptides according to the invention detected in the samples isolated from an animal and/or a human patient suffering from a liver disorder and/or epithelial cancer relative to a reference sample or relative to a reference library. The method has the additional advantage that it also provides additional and novel diagnostic parameters to characterize different subtypes of liver disorders, such as for example subtypes of HCC.

[333] The term "essentially concordant expression pattern" of the polypeptides according to the invention refers to a pattern of expression that is essentially reproducible from patient to patient or subject to subject, provided that the patients or subjects compared are in the same or comparable pathological condition or healthy condition, respectively.

[334] In another aspect of the invention it is provided a pharmaceutical composition comprising at least one compound selected from the group consisting of a polypeptide according to SEQ ID 1 to 93, a functional variant thereof, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the aforementioned vector, an antibody or a fragment of the antibody directed against one of the aforementioned polypeptides, a vector comprising a nucleic acid coding for the aforementioned antibody, a cell comprising the vector comprising a nucleic acid coding for the aforementioned antibody, and a cell comprising the vector comprising a nucleic acid coding for the aforementioned antibody fragment, combined or together with suitable additives or auxiliaries. In a preferred embodiment the pharmaceutical composition contains at least one cell according to the invention, combined or mixed together with suitable additives or auxiliaries.

[335] When compared to the state of the art of therapy of liver disorders, and/or other epithelial cancers the pharmaceutical composition according to the invention surprisingly provide an improved, sustained and/or more effective treatment.

[336] A pharmaceutical composition in the sense of the invention encompasses medicaments which can be used for preventing and/or treating liver disorders and/or epithelial cancer. The pharmaceutical composition includes, for instance, a stabilized recombinant antibody that has been produced by expression of specific antibody gene fragments in a cellular system, preferably a eukaryotic system. A recombinant antibody therapeutic for instance, is delivered by injection into the diseased liver region or into the venous or arterial vascularsystems or into the hepatic portal system. The injections can be repeated at regular intervals to achieve therapeutic efficacy. Therapeutics according this invention may also be employed in combinations with other chemical, antibody, or any other therapeutic application to improve efficacy.

[337] An antibody or other specific-binding partner can be conjugated to a second molecule, such as a cytotoxic agent, and used for targeting the second molecule to a tissue-antigen positive cell (Viteta E.S. et al, 1993, Immunotoxin therapy, in DeVita Jr. V.T. et al., eds, Cancer: Principles and Practice of Oncology, 4th ed., J.B. Lippincott Co., Philadelphia, 2624-2636). Examples of cytotoxic agents include, but are not limited to, antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, radioisotopes and chenotherapeutic agents. Techniques for conjugating therapeutic agents to antibodies are well known in prior art.

[338] In addition to immunotherapy, polynucleotides and polypeptides can be used as targets for non-immunotherapeutic applications, e.g. using compounds which interfere with function, expression, assembly of the genes according to the invention, including but not limited to modulation(s) of the enzymatic active site(s) of the polypeptide(s), change of the protein(s) structure(s), interaction(s) via small molecules, etc.

[339] The present invention also relates to a process producing a pharmaceutical composition for the treatment and/or prevention of disorders according to the invention, for example, HCC, in which at least one component selected from the group consisting of a polypeptide according to the invention, a functional variant thereof, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the aforementioned vector, an antibody or a fragment of the antibody directed against one of the aforementioned polypeptides, a vector comprising a nucleic acid coding for one of the aforementioned antibodies, a cell comprising the

vector comprising a nucleic acid coding for one of the aforementioned antibodies, and a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibody fragments, is combined or mixed together with suitable additives.

[340] The present invention furthermore relates to a pharmaceutical composition produced by this process for the treatment and/or prevention of liver disorders and/or epithelial cancers, for example, HCC, which contains at least one component selected from the group consisting of a polypeptide according to the invention, a functional variant thereof, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the aforementioned vector, an antibody or a fragment of the antibody directed against one of the aforementioned polypeptides, a vector comprising a nucleic acid coding for one of the aforementioned antibodies, a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibodies, and a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibody fragments, if appropriate together with suitable additives and auxiliaries.

[341] The invention furthermore relates to the use of this pharmaceutical composition for the prevention and/or treatment of liver disorders, for example, HCC and/or epithelial cancer.

[342] Preferably the pharmaceutical composition is employed for the treatment of a liver disorder selected from the group consisting of cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's Disease, haemochromatosis, hepatocellular carcinoma, benign liver neoplasms, and focal nodular hyperplasia. In particular the phramaceutical composition is employed for the treatment of an epithelial cancer that is an adenocarcinoma of any organ other than liver, preferably of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[343] Therapy can also be carried out in a conventional manner generally known to the person skilled in the art, e.g. by means of oral application or via intravenous injection of the pharmaceutical compositions according to the invention. It is thus possible to administer the pharmaceutical composition comprising the suitable additives or auxiliaries, such as, for example, physiological saline solution, demineralized water, stabilizers, proteinase inhibitors.

[344] A therapy based on the use of cells, which express at least one polypeptide according to the invention, functional variants thereof or nucleic acids coding for the

polypeptide, or variants thereof can be achieved by using autologous or heterologous cells. Preferred cells comprise liver cells, for example primary cultures of liver cells, liver populating stem or progenitor cells, or blood cells. The cells can be applied to the tissue, preferably to the blood or injected into the liver, with suitable carrier material. Such therapy is preferably based on the notion that upon expression and/or release of a polypeptide according to the invention the polypeptide stimulates an immune response in the patient in need of the treatment.

[345] Preferably the therapeutical approach is directed toward inhibiting the function and/or expression of at least one polypeptide according to the invention and/or the function and/or expression of at least one nucleic acid according to the invention. Such inhibition of the expression and/or function preferably reduces the expression and/or function of the targeted nucleic acid/polypeptide significantly, for example by 50%, in particular by 80% and most preferably by 95%. The inhibition of the expression and/or function preferably abolishes the expression and/or functioning of the targeted nucleic acid/polypeptide. The inhibition can occur at any level, including transcription, translation, and/or perdurance of the nucleic acid (e.g. degradation, stability) in the cell. For inhibiting the biological activity of polypeptides according to the invention e.g. antibodies and small molecules can be targeted to cell-surface, exposed, extracellular, ligand binding, functional, etc. domains of the polypeptide. The term "antagonist/inhibitor" in the sense of the present invention can be directed to, or targeted to any part of the nucleotide and polypeptide according to the invention.

[346] Such reduction or abolished expression and/or functioning of the targeted nucleic acid/polypeptide can be determined using conventional assays for determining the expression and/or functioning of a nucleic acid/polypeptide generally known to the person skilled in the art. In particular such assays for determining the function comprise methods for comparing the biological activity of the targeted nucleic acid/polypeptide before and after administration of the pharmaceutical composition. Preferably such assays for determining the expression comprise methods for comparing the level of expression of the targeted nucleic acid/polypeptide before and after administration of the pharmaceutical composition.

[347] Such therapy is preferably accomplished by the use of a nucleic acid having a sequence complementary to one of nucleic acids according to the invention, i.e. an antisense molecule or a RNA interference molecule which reduces or abolishes the translation of transcribed nucleic acids according to the invention and thereby inhibits the function and/or expression of the targeted nucleic acid/polypeptide.

[348] In a preferred embodiment, the pharmaceutical composition comprises a nucleic acid having a complementary sequence which is an antisense molecule or an RNA interference molecule.

[349] Preferably such nucleic acid having a complementary sequence may be employed in the form of a vector or a cell comprising such nucleic acid. On the polypeptide level the therapy may in particular be carried out by the use of an antibody or an antibody fragment directed against a polypeptide according to the invention. The antibody or antibody fragment may be administered directly to the patient or preferably the nucleic acid encoding the antibody is contained in a vector which is preferably contained in a cell. The cell or vector may then be administered to the patient in need of such treatment.

[350] When compared to the state of the art of therapy of liver disorders, and/or other epithelial cancers the method of treating according to the invention surprisingly provide an improved, sustained and/or more effective treatment.

[351] The invention further relates to a method of treating a patient suffering from of a liver disorder, wherein at least one component selected from the group consisting of a polypeptide according to the invention, a functional variant thereof, a nucleic acid encoding the polypeptide, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the vector, an antibody directed against the polypeptide, a fragment of the antibody, a vector comprising a nucleic acid coding for the antibody, a cell comprising the vector comprising a nucleic acid coding for the antibody, and a cell comprising the vector comprising a nucleic acid coding for the antibody fragment, optionally combined or together with suitable additives and/or auxilaries, is administered to the patient in need of a treatment in a therapeutically effective amount.

[352] Preferably the method of treatment is directed to a liver disorder selected from the group consisting of cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's disease, haemochromatosis, hepatocellular carcinoma, benign liver neoplasms, and focal nodular hyperplasia. In particular the method of treatment is directed to an epithelial cancer that is an adenocarcinoma of any organ other than liver, preferably of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[353] Methods of administering such compounds or cells have been described in detail above.

[354] The term "therapeutically effective amount" refers to the administration of an amount of the compound to the patient that results in an "effective treatment" as defined above. Determination of the therapeutically effective amount of the compound(s) is generally known to the person skilled in the art.

[355] Such methods of treating allow effective treatment of a liver disorder and/or epithelial cancers as described above.

[356] In another aspect of the invention it is provided a method of stimulating an immune response in a patient suffering from a liver disorder and/or an epithelial cancer to a polypeptide according to the invention, or a functional variant thereof, wherein at least one component selected from the group consisting of a polypeptide according to the invention, a functional variant thereof, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, and a cell comprising the aforementioned vector, is administered to the patient in need of such treatment in an amount effective to stimulate the immune response in the patient.

[357] When compared to the state of the art of therapy of liver disorders and/or other epithelial cancers, the method of stimulating an immune response according to the invention surprisingly provides an improved, sustained and/or more effective immunization.

[358] In another aspect of the invention it is provided a method of preventing a patient from developing a liver disorder and/or an epithelial cancer, wherein at least one component selected from the group consisting of a polypeptide according to the invention, a functional variant thereof, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, and a cell comprising the aforementioned vector, is administered to the patient in need of such preventive treatment in a therapeutically effective amount.

[359] When compared to the state of the art of therapy of liver disorders, and/or other epithelial cancers the method of preventing according to the invention surprisingly provides an improved, sustained and/or more effective preventive measure.

[360] Preferably the method of preventing and/or method of stimulating an immune response is directed to a liver disorder selected from the group consisting of cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's Disease, haemochromatosis, hepatocellular carcinoma, benign liver neoplasms, and focal nodular hyperplasia. In particular, preferably the method of preventing and/or method of stimulating an immune response is directed to an epithelial cancer which is an adenocarcinoma of any organ other than liver, preferably of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[361] In another aspect of the invention it is provided a method of identifying a pharmacologically active compound comprising the following steps (a) providing at least one nucleotide according to the SEQ ID 94 to SEQ ID 186, or a variant thereof, (b) contacting said nucleotide(s) with suspected to be pharmacologically active compound(s), (c) assaying the interaction of said nucleotide(s) of step (a) with said compound(s) suspected to be pharmacologically active, (d) identifying said compound(s) suspected to be pharmacologically active which directly or indirectly interact with said nucleotide(s) of step (a).

[362] In a further aspect the invention relates to a method of identifying at least one pharmacologically active compound comprising the following steps: (a) providing at least one polypeptide according to the SEQ ID 1 to SEQ ID 93, or a functional variant thereof, (b) contacting said polypeptide(s), with suspected to be pharmacologically active compound(s), (c) assaying the interaction of said polypeptide(s) of step (a) with saidcompound(s) suspected to be pharmacologically active, (d) identifying said compound (s) suspected to be pharmacologically active which directly or indirectly interact with said polypeptide(s) of step (a).

[363] Preferably said nucleotide(s) or said polypeptide(s) is (are) provided in a form selected from the group of said nucleotide(s) or said polypeptide(s) is (are) attached to a column, said nucleotide(s) or said polypeptide(s) is (are) attached to an array, said nucleotide(s) or said polypeptide(s) is (are) contained in an electrophoresis gel, said nucleotide(s) or said polypeptide(s) is (are) attached to a membrane, and said nucleotide(s) or said polypeptide(s) is (are) expressed by a cell.

[364] It is preferred but not intended to be limited to assay the interaction by a method selected from the group of enzyme and fluorescence based cellular reporter assays in which interaction of the compound suspected to be pharmacological active with a recombinant fusion protein including said polypeptide(s) of step (a) is detected. The interaction may preferably also be assayed by displacement of specific nucleic acid binding aptamer molecule(s) on the recombinant fusion protein, surface plasmon resonance, HPLC and mass spectroscopy.

[365] Preferably the direct or indirect interaction is selected from the group consisting of induction of the expression of said nucleotide(s) or said polypeptide(s), inhibition of the expression of said nucleotide(s) or said polypeptide(s), activation of the function of said nucleotide(s) or said polypeptide(s), inhibition of the function of said nucleotide(s) or said polypeptide(s).

[366] In a preferred embodiment a method for identifying an antagonist/inhibitor against the nucleotide according to the SEQ ID 94 to SEQ ID 186, or a variant thereof, comprising (a) contacting at least one nucleotide according to the SEQ ID 94 to SEQ ID 186 with a putative antagonist/inhibitor, and (b) determining whether the putative

antagonist/ inhibitor prevents the activity of the nucleotide.

[367] In a further aspect of the invention, a method for identifying a putative antagonist/ inhibitor against the polypeptide according to the SEQ ID 1 to SEQ ID 93, or a functional variant thereof, comprising (a) contacting at least one polypeptide according to the SEQ ID 1 to SEQ ID 93 with the putative antagonist/inhibitor, and (b) determining whether the putative antagonist/ inhibitor prevents the activity of the polypeptide.

[368] The term "pharmacologically active substance" in the sense of the present invention is understood as meaning all those molecules, compounds and/or compositions and substance mixtures which can interact under suitable conditions with a nucleotide according to the SEQ ID 94 to 186 or variants thereof, if appropriate together with suitable additives and/or auxiliaries.

[369] The term "pharmacologically active substance" in the sense of the present invention is also understood as meaning all those molecules, compounds and/or compositions and substance mixtures which can interact under suitable conditions with polypeptide according to the SEQ ID 1 to 93 or functional variants thereof, if appropriate together with suitable additives and/or auxiliaries.

[370] Possible pharmacologically active substances are simple chemical (organic or inorganic) molecules or compounds, but can also include peptides, proteins or complexes thereof. Examples of pharmacologically active substances are organic molecules that are derived from libraries of compounds that have been analyzed for their pharmacological activity. On account of their interaction, the pharmacologically active substances can influence the expression and/or function(s) of the nucleotide or polypeptide *in vivo* or *in vitro* or alternatively only bind to the nucleotides or polypeptides described above or enter into other interactions of covalent or non-covalent manner with them.

[371] A suitable test system, for example, that can be used in accordance with the invention is based on identifying interactions with the two hybrid system (Fields and Sternglanz, 1994, Trends in Genetics, 10, 286-292; Colas and Brent, 1998 TIBTECH, 16, 355-363). In this test system, cells are transformed with expression vectors that express fusion proteins that consist of at least one polypeptide according to the invention and a DNA-binding domain of a transcription factor such as Gal4 or LexA. The transformed cells also contain a reporter gene whose promoter contains binding sites for the corresponding DNA-binding domain. By means of transforming a further expression vector, which expresses a second fusion protein consisting of a known or unknown polypeptide and an activation domain, for example from Gal4 or herpes simplex virus VP16, the expression of the reporter gene can be greatly increased if the second fusion protein interacts with the investigated polypeptide according to the

invention. This increase in expression can be used for identifying new interacting partners, for example by preparing a cDNA library from e.g., liver tissue, or diseased liver tissue for the purpose of constructing the second fusion protein. In a preferred embodiment, the interaction partner is an inhibitor of at least one of the polypeptides according to the SEQ ID 1 to 93 (encoded by the SEQ ID 94 to 186) or functional variants thereof. This test system can also be used for screening substances that inhibit an interaction between the polypeptide according to the invention and an interacting partner. Such substances decrease the expression of the reporter gene in cells that are expressing fusion proteins of the polypeptide according to the invention and the interacting partner (Vidal and Endoh, 1999, Trends in Biotechnology, 17: 374-81). In this way, it is possible to rapidly identify novel active compounds that can be employed for the therapy of and/or prevention of liver disorders and/or epithelial cancer.

[372] Assays for identifying pharmacologically active substances that exert an influence on the expression of proteins are well known to the skilled person (see, for example, Sivaraja et al., 2001, US 6,183,956). Thus, cells that express a polypeptide according to the SEQ ID 1 for example, or functional variants thereof can be cultured as a test system for analyzing gene expression *in vitro*, with preference being given to liver cells. Gene expression is analyzed, for example, at the level of the mRNA or of the proteins using methods generally known to the person skilled in the art. In this connection, the quantity of a polypeptide according to the SEQ ID 1 to 93 (encoded by the SEQ ID 94 to 186) or mRNA present after adding one or more putative pharmacologically active substances to the cell culture is measured and compared with the corresponding quantity in a control culture. This is done, for example, with the aid of an antibody specifically directed against the polypeptide according to the SEQ ID 1 to 93 (encoded by the SEQ ID 94 to 186), or a functional variant thereof, which can be used to detect the polypeptide present in the lysate of the cells. The amount of expressed polypeptide can be quantified by methods generally known to the person skilled in the art using, for example, an ELISA or a Western blot. In this connection, it is possible to carry out the analysis as a high-throughput method and to analyze a very large number of substances for their suitability as modulators of the expression of at least one of the polypeptides according to the SEQ ID 1 to 93 (encoded by the SEQ ID 13 to 24) (Sivaraja et al., 2001, US 6,183,956). In this connection, the substances to be analyzed can be taken from substance libraries (see, e.g. DE19816414) that can contain many thousands of substances, which are frequently very heterogeneous.

[373] The invention will now be further illustrated below with the aid of the figures and examples, representing preferred embodiments and features of the invention without the invention being restricted hereto.

[374]

[375] **Figure 1 to 8 RNA expression levels in hepatocellular carcinoma (HCC) samples**

[376] Summary boxplot of expression values inHCC versus non-diseased liver cDNA microarray experiments is provided. The box plot is a graphical representation of $\log_2$ expression value ratios with the median value indicated by a horizontal line in each box. The extent of each box indicates the iqr = interquartile range (+/- 25^{th} percentile of median value); whiskers indicate of 1.5 times the iqr. Ratios that do not fall within this range are indicated with small circles. For each nucleic acid according to the invention (SEQ ID 95 to 186) elevated expression is apparent in HCC in comparison to non-diseased liver samples. For gene abbreviations see Tables 2A to 2D (**) c-syn represents three alternative nucleotide transcripts with corresponding three protein products.

[377]

[378] **Figure 9 to 99: RNA expression levels in various diseased liver samples and normal tissue(s)**

[379] Summary boxplots of expression values (SEQ ID 94 to 186) inHepatocellular Carcinoma (HCC), Focal Nodular Hyperplasia (FNH) and Cirrhosis samples (Cirrh.) versus non-neoplastic liver cDNA microarray experiments are provided. The box plot analogs are used as described in Figure 1. For each nucleic acid according to the invention, elevated expression is apparent in HCCs and most of the FNHs samples. Legend: A= HCC; B= FNH; C= Cirrh. For gene abbreviations see Table 2A to 2D (**) c-syn represents three alternative nucleotide transcripts with corresponding three protein products.

[380]

[381] **Figure 100 to 104 : Verification of differential gene expression when compared to normal tissue(s) and other types of cancer**

[382] The Assay-On-Demand (Applied Biosystems, USA) quantitative PCR (Q-PCR) method is utilized for verification of disease deregulated expression of nucleic acids PACE4; BIGH3; s.t.OCIA; SDCCAG28; Rab2; TM4SF4; DAD-1. In Figures 100 to 103, for example, the following commercially available Assay-On-Demand primers are employed: Hs00159844_m1 for PACE4 (SEQ ID 98); Hs00154671_m1 for BIGH3 (SEQ ID 99); Hs00215197_m1 for s.t.OCIA (SEQ ID 101); Hs00246405_m1 for SDCCAG28 (SEQ ID 102); Hs00234094_m1 for Rab2 target (SEQ ID 106), Hs00270335_m1 for TM4SF4 (SEQ ID 112); Hs00154671_m1 for DAD-1 (SEQ ID 140). In another example (Figure 104), the AKR1C1 PCR product is monitored accordingly by incorporation of fluorescent double-stranded DNA intercalating molecules such as SYBR green. The increased expression of AKR1C1 (SEQ ID 96) in

HCC when compared to normal liver (NNL) is verified by using the SEQ ID 199 and SEQ ID 200 primers; data for B and C are not available. Overall, Mann-Whitney-U Test (non-parametric test applied for non-normally distributed data) is performed as Wilcoxon Rank Sum Test (Hollander & Wolfe, 1973, Nonparametric statistical inference. New York: John Wiley & Sons, pgs. 27-33, 68-75; Bauer, D.F., 1972, J. Amer. Statistical Assoc. 67, pgs 687-690). The expression values typically do not fit to a normal distribution so averaging the values may be misleading. However, analysis of the median values demonstrates significant differences in most of the cases between experimental and reference values, particularly in the large data sets.

[383] Legend: A= Hepatocellular Carcinoma (HCC); B= Focal Nodular Hyperplasia (FNH); C= Cirrhosis (Cirrh.); D= Non-Neoplastic liver (NNL). For gene abbreviations see Table 2A to 2D.

[384] **Figure 105: SDCCAG28 protein expression in tissues**

[385] Protein extracts are subjected to immunoblot analysis with HuCAL™ antibodies (Morphosys AG, Germany) specific to recombinant SDCCAG28 protein (e.g., MOR3491 anti ORI010), in order to determine the level of expression of the protein in human tissues [a= ORI010 (human SDCCAG28 recombinant protein); b= Hepatocellular Carcinoma (HCC); c= Normal Liver (NL); d= hepatoma HepG2 cell line. Annotated 33kDa position reflects a size of the predicted SDCCAG28 protein. Following incubation with an anti-HIS mouse antibody to specifically detect the HuCAL™ antibody and a horse-radish peroxidase (HRP) conjugated anti-mouse antibody the immune complexes are detected with a chemiluminescent HRP substrate. It is evident that the native SDCCAG28 protein migrates slightly faster than the recombinant SDCCAG28 protein (approximately 44 kDa band in lane a compared with 40.5 kDa bands prominent in lanes b and d). The intensities of the SDCCAG28 protein band are clearly stronger in the HCC tissue and in the HepG2 hepatoma cell line lysate (lanes b and d, respectively) than in the normal liver tissue (lane c). These analyses indicate that SDCCAG28 protein, the functional product of the SDCCAG28 mRNA specifically upregulated in HCC, is also highly overexpressed in HCC when compared to NNL.

[386]

[387] **Figure 106 to 107: Expression of HCC deregulated genes correlates with proliferation of hepatoma cells**

[388] Proliferation-dependent expression of target gene sequences according to the invention in hepatoma cells Hep3B (Figure 106) and HepG2 (Figure 107) following serum stimulation for 8 hours (black columns) and for 12 hours (white columns) of quiescent cells. The $\log_2$-transformed ratios of serum-stimulated vs. quiescent expression values from cDNA microarray experiment readout are provided. The

substantial increase in the level of expression of these sequences (for example, (ZNF216) SEQ ID 95; (AKR1C1) SEQ ID 96; (PACE4) SEQ ID 98; (SDCCAG28) SEQ ID 102; (TMP21) SEQ ID 104 and (RAB2) SEQ ID 106) in proliferating compared to quiescent hepatoma cells suggests that elevated expression of these sequences is functionally significant for liver cancer cell growth. For gene abbreviations see Table 2A to 2D.

[389]

[390] **Figure 108 to 109: Effect of dUT specific inhibitor on growth of proliferating liver cancer (hepatoma) cell lines**

[391] Specific dUT enzyme inhibitor (DMT-dU (5'-O-(4,4'-Dimethoxytrityl)-2'-deoxyuridine) (Sigma; No. D7279) is added to the hepatoma cells (Hep3B in Figure 108 and HepG2 in Figure 109) at the 10, 25, 50, 100, 250 and 500 μM final concentrations in a maximum of 3 μl of the appropriate solvent. Following incubation of the cells for 24 (black columns) and 48 hours (white columns) respectively, cell viability is assessed via an MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) reduction assay known in the prior art (CellTiter 96 Aqueous One Solution Cell Proliferation Assay; Promega), and plotted relative to the number of cells in wells not treated with the inhibitor (control = 0; no inhibitor added). The relationship between the increased concentration of the inhibitor and absorbance (A= 495nm) reflects the Hep3B/ HepG2 cytostatic/ anti-proliferative response, suggesting that dUT gene correlates with human liver tumor cell proliferation.

Examples

[392]

[393] **Example 1: Preparation of HCC subtracted cDNA libraries**

[394] RNA is isolated from three pathologist-confirmed HCC tumor samples and from three pathologist-confirmed non-diseased human liver samples using the TRIZOL reagent (Invitrogen) according to standard methods (Chomczynski & Sacchi, 1987, Anal. Biochem. 162:156-159). The tissues used for the generation of cDNA libraries is from patients that provided specific informed consent for utilization of this material for research purposes, including commercial research. mRNA is converted to double stranded cDNA with reverse transcriptase and DNA polymerase as described in the instructions provided in the "PCR select cDNA subtraction kit" from Clontech Laboratories. To enrich for cDNAs specifically increased and decreased in HCC, cDNAs expressed in common and at similar levels in the reference liver pool and in HCC are removed by subtractive suppressive hybridization (SSH) according to the instructions provided in this kit and as described by Diatchenko et al. (1996, Proc. Natl. Acad. Sci.

USA 93:6025-6030). The SSH steps are performed in both directions (subtracting non-diseased liver cDNAs from HCC cDNAs and subtracting HCC cDNAs from non-diseased liver cDNAs) so the resulting cDNA molecules represent nucleic acid sequences both up- and down-regulated in HCC but do not represent those that are not differentially expressed. In addition a normalized but not subtracted HCC cDNA library is generated to better represent rare mRNA transcripts in HCC tissues. These cDNAs are separately cloned into the pCRII vector (Invitrogen) by ligation into this plasmid followed by electrophoretic transformation into *E. coli* XL-1-Blue electroporation-competent cells (Stratagene). The cloning is carried out as described by the supplier of the vector and competent cells. Cloned differentially expressed cDNAs are plated onto selective (ampicillin) media to isolate individual clones. 960 clones are isolated from each SSH library and 384 clones isolated from the normalized HCC library and cultures established in 96-well microtiter plates. Together these cDNA clones provide a unique representation of mRNA expression specific for human HCC tissue.

[395]

[396] **Example 2: Preparation and hybridization of HCC cDNA microarrays**

[397] 1 ml cultures of the SSH cDNA library clones described above are established and the cDNA inserts amplified by PCR with primers specific to the vector sequence flanking the cDNA inserts. The M13 forward (5'- gtaaaacgacggccag-3'; SEQ ID 42) and M13 reverse primers (5'-caggaaacagctatgac-3'; SEQ ID 43) are employed for the PCR amplification of clone inserts. Fifty microliters of the bacterial cultures are heat denatured at 95°C for 10 minutes, debris removed by centrifugation, and 2 µl of the supernatant included in a standard PCR [1X Amplitaq PCR buffer, 2.5 mM $MgCl_2$, 37.5 nM each primer, 0.5 mM each of dATP, dCTP, dGTP and dTTP and 1.5 units Amplitaq DNA polymerase (Applied Biosystems)]. Reaction conditions are 95°C for 5 minutes followed by 35 cycles of: 94°C for 30 seconds, 60°C for 30 seconds, 72°C for 60 seconds; then followed by 72°C for 7 minutes and then cooled to 4°C. Amplification of cDNA inserts is confirmed by electrophoresis of a 5% of the PCR on a 1% agarose gel comprising 0.4 mg/ml ethidium bromide and run in 1X Tris Acetate EDTA (TAE; 40mM Tris-acetate, 1mM EDTA, pH 7.5) buffer. Each of the SSH clone amplified insert sequences is affixed to sialinized glass microscope slides (GAPS Corning) using a GeneticMicrosystems 417 cDNA arrayer robot to generate custom HCC cDNA microarrays. The protocol for spotting the cDNA inserts to the slides is according to that published by Hedge et al. (2000, Biotechniques 29:548-560) except that PCR products are spotted directly from the PCR microtiter plates without purification or adjustment of the cDNA buffer. In addition to the SSH cDNA clone inserts, numerous control DNAs are spotted onto the microarrays as controls for hybridization reactions. Further,

approximately 2000 publicly available cDNA clones corresponding to genes previously reported to be involved in cancer are purchased from the German Genome Research Center (RZPD), expanded, amplified and spotted onto these microarrays as described above. For preparation of hybridization probes, 20 micrograms of RNA from additional pathology-confirmed liver disorders and from the same quantity of pooled non-diseased liver RNA is converted to cy5-fluorescence-labeled and cy3-fluorescence-labeled cDNA, respectively (cy5-CTP and cy3-CTP, Pharmacia) using reverse transcriptase according to the standard methods (Hedge et al., 2000, Biotechniques 29: 548-560). Using this protocol, these labeled cDNAs are competitively hybridized to the HCC microarrays. Following prehybridization at 42°C for 45 minutes in 5X SCC (0.75 M sodium citrate, 75 mM sodium citrate, pH 7.0); 0.1% SDS (sodium dodecyl sulfate) and 1% BSA (bovine serum albumin), the hybridization is carried out overnight at 42°C in buffer comprising 50% formamide, 5XSSC, and 0.1% SDS. Hybridized slides are washed in stringent conditions (twice at 42°C in 1X SSC, 0.1% SDS for 2 minutes each; twice at room temperature in 0.1X SSC, 0.1% SDS for 4 minutes each; and twice at room temperature in 0.05X SSC for 2 minutes each), dried and analyzed with the GeneticMicrosystems 418 cDNA microarray scanner and associated Imagene 4.1 image analysis software according to the manufacture's recommendations.

[398]

[399] **Example 3: Independent verification of differential expression of the nucleic acids and polypeptides according to the invention**

[400] RNA is isolated from human patient samples as described in detail above. HCC samples for this analysis are not from the same patients as employed for production of the HCC SSH library or for cDNA microarray chip hybridization. In addition to HCC samples, RNA is prepared from independent non-diseased liver samples to assess expression of the nucleic acids according to the invention in non-diseased liver tissue. Further, RNA is prepared from additional non-diseased and cancer tissues to assess expression of the nucleic acids according to the invention in other normal human tissues and other human cancers.One mg of RNA is converted to single-strand cDNA with the aid of Superscript reverse transcriptase (Invitrogen) in dATP, dCTP, dGTP, and dTTP (0.4 mM each), 7.5 nM random 6-nucleotide primer (hexamers), 10 mM dithiothreitol and 1 unit RNAse inhibitor using standard procedures known in the art (Sambrook et al., Molecular Cloning, 2nd ed., 1989, Cold Spring Harbor Press, NY, USA, pp. 5.52-5.55). The presence or absence and the relative concentration of the nucleic acids according to the invention is then confirmed and verified by amplification of these sequences from the cDNA with primer pairs specific to each nucleic acid according to the invention in quantitative kinetic PCR experiments. The

Assay-On-Demand (Applied Biosystems, USA) quantitative PCR method well known for the person skilled in the art might be utilized for verification of disease deregulated expression of nucleic acids according to the invention (Figure 3A/3B). For example, the Assay-On-Demand ID primer numbers for PACE 4, BIGH3, s.t.OCIA, SDCCAG28, Rab2, PRKAR1A, PRDX1, IQGAP2, TM4SF4, DAD-1 target genes are given in the following **Table 8**.

[401]

[402] **Table 8: Target clones and their Assay-On-Demand ID**

Table 8

Gene	Assay ID (Catalogue Number)
PACE4	Hs00159844_m1
BIGH3	Hs00154671_m1
s.t.Ocia	Hs00215197_m1
SDCCAG28	Hs00246405_m1
Rab2	Hs00234094_m1
PRKAR1A	Hs00267597_m1
PRDX1	Hs 00602020_m1
IQGAP2	Hs00183606_m1
TM4SF4	Hs00270335_m1
DAD-1	Hs00154671_m1

[403]

[404] In further example, AKR1C1 PCR product is monitored accordingly by incorporation of fluorescent double-stranded DNA intercalating molecules such as SYBR green. The AKR1C1 cDNA is validated by using following primers: AKR1C1-p1, 5'- ttggaaaggtcactgaaaaatct-3' (SEQ ID 199) and AKR1C1-p2, 5'-gctggctgcggttgaagttgg-3' (SEQ ID 200) verifying the specific expression of this gene (SEQ ID 96) in HCCs when compared to normal liver samples (Figure 104).

[405] Usally PCR is performed according to the manufacturer's instructions using TaqMan Universal PCR Mastermix (Cat.Nr. 4304437; Applied Biosystems, Branchburg, New Jersey USA). Kinetic quantitative PCR analyses are performed by using the 7000 Sequence Detection System (Applera). The PCR Setup included two reference genes [GAPDH and ßeta-Actin (GAPDH primers used = GAPDH-p1, SEQ ID 187; GAPDH-P2, SEQ ID 188; GAPDH-p3, SEQ ID 189) (ß-Actin primers used = ßActin-p1, SEQ ID 190; ßActin-p2, SEQ ID 191; ßActin-p3, SEQ ID 192)] which are used for independent normalisation of the investigated target genes. A standard curve

(125ng, 25ng, 5ng and 1ng) is used for proper calculation of the expression data. The PCR sample contained 12.5 ng of cDNA, 12.5 µl Universal PCR Mastermix and 1.25µl Assay-On-Demand reagent to give a final volume of 25µl. PCR conditions are used according to the manufacture's instructions (2 min 50°C, 10 min 95°C followed by 40 cycles of 15 sec 95°C and 1 min at 60°C). Amplification of cDNA inserts is additionally confirmed by electrophoresis of a 10% of the PCR on a 2.5% agarose gel comprising 0.5 mg/ml ethidium bromide and run in 1X Tris Acetate EDTA (TAE) buffer. Standard controls for RT-PCR including RNAse treatment of samples prior to cDNA synthesis and omission of reverse transcriptase routinely demonstrate the specificity of these reactions. The kinetic quantitative RT-PCR (Q-PCR) verifies the over expression of sequences according to the invention in liver cancer and other liver disorder relative to non-diseased liver (Figures 100 to 104).

[406] Furthermore, the protein expression analyses indicate that for example SDCCAG28 protein, the functional product of SDCCAG28 mRNA specifically upregulated in HCC, is also significantly overexpressed in HCC (Figure 105). To detect SDCCAG28 protein expression in HCC samples standard western blot analysis known in the prior art is performed using protein extracts derived from frozen tissues (stored in liquid nitrogen). The 50 µm sections are obtained (HCC, normal liver) using a refrigerated microtome (cyrocut, Leica CM3050), wherein the identity and homogeneity of the tissues under scrutiny is verified by H&E-staining of sections taken before, in between and after each cutting process. Tissues sections (HCC, normal liver), SDCCAG28 antigen (Morphosys AG, Germany) and HepG2 cells are resuspended in ice-cold RIPA-buffer (50 mM Tris-HCl pH 7.4, 250 mM NaCl, 0.1% SDS, 1% deoxycholate, 1% NP-40) supplemented with 2 µg/ml leupeptin, 2 µg/ml pepstatin, 2 µg/ml aprotinin, 1 mM phenylmethylsulfonylfluoride (PMSF), and 2 mM dithiothreitol followed by homogenization through sonication (2 bursts of 5 seconds) on ice. After incubation for 20 minutes on ice, the lysates are cleared by two centrifugational steps in a microcentrifuge at 13 000 rpm for 15 minutes at 4°C and the supernatants are collected. Protein concentrations are determined by the Bradford assay(Biorad) using bovine serum albumin as a standard. Equal amounts of protein (typically 10-30 µg) are separated on a 12% SDS-PAGE gel and transferred electrophoretically to a polyvinylidene diflouride (PVDF) membrane (Hybond-P, Amersham Biosciences) through Semidry-blotting (TE 70, Amersham). The membrane is blocked for 1 hour (or overnight) at room temperature in blocking solution [5 to 10% milkpowder (Micrbiology/Lactan:1.15363.0500) in TBS-T (25 mM Tris-HCl pH 7.4, 137 mM NaCl, 3 mM KCl, comprising 0.1% Tween-20 (Merck: 822184) and 2% BSA (Sigma:A-7906)] and incubated with the primary antibody specific for the SDCCAG28 recombinant protein (Morphosys AG, Germany), usually in the concentration between

30ng to 50ng/ml in TBS-T/1% milk solution at 4°C overnight with agitation. After removal of the primary antibody solution and several washes in TBS-T, the membrane is incubated with a mouse anti-HIS antibody to specifically detect the primary antibody (Dianova, 1:25000) followed by a rabbit anti-mouse HRP (horse-radish peroxidase)-conjugated antibody (Dako, 1: 1000) for one hour at room temperature. Following several washes in TBS-T, detection is performed through chemiluminiscence (ECL, Amersham) detection of HRP activity and exposing the membrane to x-ray film.

[407] These data provide independent verification of deregulated expression of the nucleic acids and polypeptides according to the invention in HCC. Expression of the nucleic acids and polypeptides according to the invention is either absent or observed only at very low levels in non-diseased liver, thereby validating the differential expression of these nucleic acids identified by hybridization to the cDNA microarray. The results provide surprising evidence that the nucleic acids and polypeptides according to the invention can be used to diagnose, prevent and/or treat disorders according to the invention.

[408]

[409] **Example 4: Sequences according to the invention are increased in proliferating liver cancer (hepatoma) cell lines**

[410] Human hepatoma cell lines (Hep3B, HepG2) are cultured in DMEM supplemented with 10% fetal bovine serum (FBS) in a humidified incubator with 5% CO_2 at 37°C. The cells are split to about 20% confluency and subsequently rendered quiescent by culturing in the absence of serum for 3 days. After the starvation period, the cells are stimulated to proliferate by the addition of 10 % FBS to the media. Samples are taken before and following the induction of cell growth (0, 8 and 12 hours) for the preparation of RNA and for determination of the position of the cells in the cell cycle by FACS (fluorescence activated cell sorting) analysis. Accordingly, to determine the cell cycle distribution by propidium iodide (PI) staining, the cells are harvested by trypsinization, washed twice with phosphate buffered saline (PBS) and finally resuspended in 500 µl PBS. Subsequently, 5 ml prechilled methanol is added. After 10 minutes incubation at -20°C the cell suspension is directly used for FACS analysis following 3 times washing in PBS, resuspended in 500 µl propidium iodide (PI) staining buffer (DNA-Prep Stain, Part No. 6604452; Beckman Coulter) and incubated for 15 minutes at 37°C. Finally, 70 µl of 1M NaCl is added and the samples are kept on ice protected from light prior to analysis on an EPICS XL-MCL flow cytometer (Beckman Coulter). Cells prepared from an asynchronous cell population are used as reference.

[411] The isolated RNA is used to monitor the expression of genes in quiescent vs. pro-

liferating hepatoma cells by cDNA microarray analysis. Following labeling with fluorescent dyes as described in example 2, the RNAs are hybridized on a specifically developed HCC- specific cDNA microarray chip that also contained control genes which are known to be expressed in a cell cycle dependent manner. Finally, the data are analysed using ImaGene 4.1 and GeneSight software packages. The signals obtained for 0 hours samples isolated before the addition of serum are used as reference. The $\log_2$-transformed ratios of serum-stimulated vs. quiescent expression values from the cDNA experiment readout is provided in Figure 106 to 107.

[412] These data indicate that the sequences according to the invention are correlated with human liver tumor cell proliferation. Compared to the state of the art, these nucleic acids and polypeptides therefore surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis of the liver disorders and/or epithelial cancers.

[413]

[414] **Example 5: Effect of dUT specific small molecule inhibitor on growth of proliferating liver cancer (hepatoma) cell lines**

[415] To determine the effects of small molecule inhibitors of activity of enzyme polypeptides according to the invention on the growth of human hepatoma cells, for example a specific dUT inhibitor (DMT-dU (5'-O-(4,4'-Dimethoxytrityl)-2'-deoxyuridine) (Sigma; No. D7279) is employed. Hep3B or HepG2 cells are seeded into 96-well plates at 10,000 and 7,500 cells, respectively, in a total volume of 150 µl of growth DMEM media supplemented with 10% fetal calf serum. The next day of incubation at 37 °C, the dUT enzyme inhibitor is added to the cells at the 10, 25, 50, 100, 250 and 500 µM final concentrations in a maximum of 3 µl of the appropriate solvent. Following incubation of the cells for 24 and 48 hours, cell viability is assessed via an MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) reduction assay known in the prior art (CellTiter 96 Aqueous One Solution Cell Proliferation Assay; Promega) according to the manufacturer's instructions. Thirty µl of the assay reagent are added directly to the culture wells, incubated for 1-2 hours and then absorbance at 495 nm is recorded using a microtiter plate reader (Anthos 2010; Anthos Labtec Instruments). Each value represents the mean of at least 4 replicates. Control cells (= 0) receive solvent only (Figures 108 to 109)

[416] The relationship between the increased concentration of the inhibitor and absorbance indicates that application of the aforementioned specific dUT inhibitor to hepatoma cells elicits a cytostatic/ anti-proliferative response, suggesting a specific role of the dUT gene in human liver tumor cell proliferation.

[417]

[418] **Example 6: Elevation of enzymatic activity in hepatoma cells correlates with**

AKR1C1 target gene overexpression in liver disorders

[419] A comparison of the enzymatic activity of a target gene encoded polypeptide gives insight whether a deregulation of mRNA transcript is also reflected by a significant increase in activity that indicates its functional role in tumor biology. In a substrate-specific reaction, the activity of AKR1C1 (SEQ ID 96) is determined (see below Table 9).

[420] Enzymatic assays are performed by using lysates prepared from frozen tissues (stored in liquid nitrogen) or from cell pellets derived from asynchronously growing human hepatoma cell lines (Hep3B, HepG2). 50 µm sections obtained from pieces of frozen tissues using a freezing microtome (Cryocut, Leica CM3050) and the identity and homogeneity of the tissues under scrutiny is verified by a pathologist following H &E-staining of sections taken before, in between, and after each cutting process. Tissues sections as well as frozen cell pellets are resuspended in ice-cold lysis buffer (50 mM KPO_4 pH 7.0, 10 mM KOAc, 2 mM $MgCl_2$) supplemented with 2 µg/ml leupeptin, 2 µg/ml pepstatin, 2 µg/ml aprotinin, 1 mM phenylmethylsulfonylfluoride, and 2 mM dithiothreitol followed by homogenization through sonication (2 bursts of 3 seconds) on ice. After incubation for 15 minutes on ice, the lysates are cleared by two centrifugation steps in a microcentrifuge at 13,000 rpm for 15 minutes at 4°C and the supernatants are collected. Protein concentrations are determined by the Bradford assay (Biorad) using bovine serum albumin as a standard.

[421] The AKR1C1 enzymatic activity is measured spectrophotometrically based on the oxidation of 1-acenaphthenol in 1.0 ml systems containing 1 mM 1-acenaphthenol (in 4% methanol), 2.3 mM NAD^+, and various amounts of whole cell lysate in 100 mM potassium phosphate buffer (pH 7.0). Reactions runs at 25°C wherein the change in absorbance of pyridine nucleotide over time is monitored at 340 nm on a Beckman DU640 spectrophotometer. Absorbance values are plotted versus time, and slope-values versus time (min^{-1}) are calculated from initial reaction velocities using linear least-squares regression analysis, see Table 9 (HCC = Hepatocellular Carcinoma; NNL = Non-Neoplastic (Normal) Liver).

[422]

[423]

[424]

[425]

[426] **Table 9: Enzymatic assay for AKR1C1 (SEQ ID 96)**

[427]

Table 9

Tissue	Protein con-	Slope	Weighted Mean of

	centration [µg]	time $^{-1}$ [min $^{-1}$]	the slope [min $^{-1}$]
NNL1	100	0.0048	0.0043
	200	0.0076	
NNL2	100	0.0057	0.0054
	200	0.0102	
HCC11	100	0.0130	0.0127
	200	0.0247	
HCC28	100	0.0097	0.0095
	200	0.0187	
HCC30	100	0.0334	0.0317
	200	0.0599	
HCC2	100	0.0136	0.0102
	200	0.0137	
HCC13	100	0.0158	0.0128
	200	0.0197	

[428]

[429] The HCC samples (HCC11, HCC28, HCC30 and HCC2) are characterized by a weighted mean of the slope approximately 2-3-fold higher than the NNL samples. These data clearly show the correlation between the upregulation of AKR1C1 gene transcript in HCC with the induction of the AKR1C1 enzymatic activity in hepatoma cell lines, suggesting that the sequences according to the invention are correlated with human liver tumor cell proliferation. Compared to the state of the art, these nucleic acids and polypeptides therefore surprisingly allow improved, more sensitive, earlier, faster, and/or non-invasive diagnosis of the liver disorders and/or epithelial cancers.

[430]

[431]

[432] **Example 7: A method of diagnosing using HCC specific probes**

[433] A diagnostic method for disorders according to the invention preferably based on the polymerase chain reaction (PCR) can be established. A standard PCR detection of nucleic acid sequences of the invention can be sufficient to identify, for example, circulating HCC tumor cells in the blood stream of the patient. Detection of expression of nucleic acid sequences of the invention in tumor biopsy material however, such as from a fine needle biopsy, would also be a preferred indication for this diagnostic

procedure. Nucleic acid sequences of the invention, ZNF216 (SEQ ID 95) for example, are not detected in most non-diseased tissues and relatively specifically expressed in e.g. HCC. Elevated expression of this nucleic acid in FNH and HCC is also demonstrated indicating the potential discriminatory power of such an approach for differential diagnosis of liver diseases (Figures 1 and 9; Tables 3A/4A).

[434] The PCR diagnostic would preferably require approximately 1 pg, preferably at least 100 ng, more preferably at least 1 µg of RNA isolated from patient material. In the preferred utilization the RNA would be isolated according to standard procedures from, e.g., the white blood cell fraction preferably from circulating blood obtained by the minimally invasive venupuncture procedure. In this preferred case, the procedure would detect the presence of HCC tumor cells in the blood circulatory system. RNA could similarly be isolated from liver or other tissue biopsy material.

[435] For specific detection of ZNF216, the PCR diagnostic would include several primers specific for ZNF216 nucleic acid sequence, including a specific primer set for cDNA synthesis from the RNA generated from the patient sample, such as for example (ZNF216-p1, 5'-ttctttctgcacatgaaacatctg-3' (SEQ ID 195). Also included would be forward and reverse PCR primers specific for ZNF 216 nucleic acid sequence such as for example, ZNF216-p2, 5'-gagaggacaaaataactaccc-3' (SEQ ID 196) and ZNF216-p3, 5'-caattcaggagctttttcttca-3' (SEQ ID 197), and for increased specificity and heightened sensitivity a fluorescently-labeled hydrolysis probe would be included such as, for example, ZNF216-pr, 5'-tactgggctgagaaactgatggactgggctga-3', SEQ ID 198 (from nucleotide 694 to 663 of the SEQ ID 95 reverse strand). The specificity of this detection assay may be further heightened with alternative primers specific for the ZNF216 sequence including an independent pair of specific PCR forward and reverse primers ("nested" primers) located on the amplicon of the outer forward and reverse PCR primers. In this case the probe primer would be specific for the amplicon the nested PCR primer pair.

[436] Quantitative assessment of AKR1C1 mRNA levels, for example, may also be achieved in such detection strategies as illustrated in Figure 3C using kinetic quantitative PCR with, for example:

[437] cDNA may be prepared from the patient RNA sample following digestion of the RNA with RNAse-free DNAse-1 (Roche) to eliminate potential contamination by genomic DNA. This contamination possibility is further controlled by including primers for PCR amplification from sequences of different exons of the gene such that PCR products resulting from a genomic DNA template (and thereby not reflective of expression of the mRNA corresponding to for example ZNF216) would be larger than the RNA specific PCR products. cDNA synthesis can e.g. be primed by the ZNF216-specific ZNF216-p1 (SEQ ID 195;at about 1 µM) with the aid of reverse tran-

scriptase [such as Maloney murine leukemia virus reverse transcriptase (Roche) at about 2 unit/reaction] in an appropriate buffer such as 50 mM Tris-HCl, 6 mM MgCl2, 40 mM KCl, and 10 mM dithiotreitol, pH 8.5. Also required in the cDNA synthesis reaction is dATP, dCTP, dGTP and dTTP, each at about 1 mM, RNAse inhibitor, such as placental RNAse inhibitor (Roche) at about 1-10 units/reaction. cDNA synthesis would be preferably carried out at 42°C for 30 to 60 minutes followed by heating at 95° C for 10 minutes to denature the RNA template. The resulting cDNA can be employed as the template for a PCR to detect ZNF 216 in the blood (or liver or tissue biopsy sample). The additional reagents required for PCR detection of ZNF216 would preferably also be provided including: 10X Taq DNA polymerase buffer (500 mM Tris-Cl pH 8.3, 25 mM $MgCl_2$, 0.1% Triton X-100); a mixture of dATP, dCTP, dGTP and dTTP for a final concentration of 0.2 mM each; Taq DNA polymerase (2.5U/reaction), and ZNF216 specific primers such as ZNF216-p1 (SEQ ID 195), ZNF216-p2 (SEQ ID 196) and ZNF216-p3, (SEQ ID 197), and for increased specificity and heightened sensitivity a fluorescently-labelled hydrolysis probe ZNF216-pr, SEQ ID 198 (0.1 - 1 μM final concentration). A positive control for PCR amplification such DNA from a plasmid clone with the ZNF216 sequence insert would preferably also be included (1-10 ng/reaction). The PCR can e.g. be carried out over 22-40 cycles of 95°C for 30 seconds, 60°C for 30 seconds, 72°C for 60 seconds. As indicated above, preferred additional sensitivity and specificity may be achieved in this diagnostic procedure by utilization of the additional ZNF216primer set located within the sequence amplified with the original PCR primer set. In this case a subsequent PCR under conditions similar to those utilized in the first PCR reaction except that would be employed to amplify the nested sequence in a reaction that included 1-10 μl of the first PCR as the template DNA. Alternatively, the reaction may preferably be carried with the first primer set for 10-15 cycles after which and 1-10 μl of this reaction then included as template in a new PCR reaction with nested primers (and including all the necessary PCR components). Detection of ZNF216 specific PCR product(s) should preferably utilize agarose gel electrophoresis as is known in the art and described in previous examples. Included in the diagnostic should preferably be a comparable fluid or tissue extract as a control for such PCR-based diagnostic test. This may include serum or plasma from non-diseased individuals and/or serum, plasma or tissue extracts from an appropriate animal model. If the PCR-determined expression of the nucleic acid according to the invention such as the product of the reaction with primers ZNF216-p1 (SEQ ID 195), ZNF216-p2 (SEQ ID 196) , ZNF216-p3 (SEQ ID 197) and ZNF 216-pr (SEQ ID 198) is upregulated in the sample isolated from the patient relative to the control and if in particular the upregulated expression essentially matches the disorder specific (mean) expression ratios then such matching is indicative

of the patient suffering from the disorder. Variations on this approach can also be appreciated. The cDNA synthesis and PCR amplifications can be carried our sequentially or simultaneously in a single reaction vessel utilizing heat stabile DNA polymerases with reverse transcriptase activities, such as provided by the Titan one-tube or *Carboxydothermus* DNA polymerase one-set RT-PCR systems from Roche. Alternatively the PCR product can be monitored by incorporation of fluorescently labeled primers or various fluorescence-based indicators of PCR product including the Taqman probe hydrolysis systems, as described above and with fluorescent double-stranded DNA intercalating molecules such as SYBR green. The fluorescent-based approaches provide advantage as the accumulation of PCR product can be continuously monitored to achieve sensitive quantitative assessment of expression of the nucleic acid according to the invention. This should be particularly advantageous for nucleic acids increased in blood or tissues of disorders according to the invention but also present at lower levels in non-diseased patients and tissues such that quantitative information about the level of expression of the nucleic acid is acquired. Further, as with this example, accurate quantitation of nucleic acid expression levels contributes to differential diagnosis, between cirrhosis and HCC for example. Comparison of this data with supplied standards indicative of disease and absence of disease provides an important advantage for such a diagnostic procedure.

[438] Additional variations on this diagnostic strategy include simultaneous detection of multiple nucleic acids according to the invention and/or of nucleic acids according to the invention together with other nucleic acids implicated in the disorder. Further hybridization-based diagnostic detection of nucleic acids according to the invention is also envisioned. In this case mRNA detection preferably utilizing detection of RNA transferred to a membrane by capillary or electrophoretic blotting, RNAse protection or in situ hybridization on patient cells or tissue biopsy samples is also effective.

[439] By similar methods and variants thereof the nucleic acids according to the invention and/or of nucleic acids according to the invention together with other nucleic acids can be utilized for diagnosis of the disorders according to the invention.

[440]

[441] **Example 8: A method of diagnosing via antibody detection of polypeptides according to the invention**

[442] A preferred diagnostic method for disorders according to the invention is based on antibodies directed against a polypeptide according to the invention. For example, a diagnostic procedure may preferably employ serum detection of specific upregulated gene proteins via enzyme-linked immunosorbent assay (ELISA) assay. In a simple form the diagnostic assay preferably includes a microtiter plate or strip of microtiter wells, e.g., thoroughly coated with an isolated and purified antibody specific to a

polypeptide according to the invention such as, ZNF216 (SEQ ID 2), AKR1C1 (SEQ ID 3). The antibody may for example be an affinity purified polyclonal antibody, such as is commonly raised in rabbits, for example, or a purified monoclonal antibody such as is commonly produced in mice according to procedures well established in the art (Cooper, H.M. & Paterson, Y., (2000), *In* Current Protocols in Molecular Biology (Ansubel, F.A. et al., eds.) pp. 11.12.1 – 11.12.9, Greene Publ. & Wiley Intersci., NY); (Fuller S.A. et al., (1992), *In* Current Protocols in Molecular Biology (Ansubel, F.A. et al., eds.) pp. 11.4.1 – 11.9.3, Greene Publ. & Wiley Intersci., NY). Preferably, the antibody may a recombinant antibody obtained from phage display library panning and purification as has been described by Knappik et al. (2000, J. Molec. Biol. 296:57-86) or by Chadd and Chamow (2001 Curr. Opin. Biotechnol.12:188-94), or a fragment thereof. The antibody coating is preferably achieved by dilution of the anti-ZNF216.pr antibody or anti-AKR1C1.pr antibody to 1-100 µg/ml in a standard coating solution such as phosphate buffered saline (PBS). The antibody is preferably bound to the absorptive surface of the microtiter well (such as a Nunc Maxisorp immunoplate) for 60 minutes at 37°C, or overnight at room temperature or 4°C. Prior to binding sample to the coated wells, the wells are preferably thoroughly blocked from non-specific binding by incubation for 15-60 minutes at room temperature in a concentrated protein solution such as 5% bovine serum albumin in phosphate buffered saline or 5% non-fat dry milk powder resuspended in the same buffer. Preferably, the patient sample material is then applied to the microtiter wells, diluted into the blocking solution to increase specificity of detection. The sample may be for example plasma or serum or protein extract from tissue biopsy or surgical resection prepared according to methods well known in the art (Smith, J.A. (2001) *In*, Current Protocols in Molecular Biology, Ausubel, F.A. et al., eds) pp. 10.0.1- 10.0.23, Greene Publ. & Wiley Intersci., NY). In particular, the patient sample is brought into contact with the antibody-coated well for 30-120 minutes (or longer) at room temperature or at 4°C. Non-specifically interacting proteins are preferably removed by extensive washing with a standard wash buffer such as 0.1 M Tris-buffered saline with 0.02-0.1% Tween 20, for example. Washes are preferably carried out for 3-10 minutes and repeated 3-5 times. Detection of ZNF216 polypeptide in the patient sample is for example achieved by subsequent binding reaction with a second, independent anti-ZNF216 antibody, generated as described above, recognizing a distinct epitope on the ZNF216 polypeptide in the standard two-site 'sandwich' type ELISA. Binding of the second anti-ZNF216 antibody or AKR1C1 antibody is for example achieved by incubating the wells in the antibody (at a concentration of 1-100 µg/ml in blocking solution, for example) at room temperature for 30-60 minutes followed by extensive washing as in the previous step. The second antibody may preferably be directly coupled to an enzyme capable of producing a

colorigenic or fluorgenic reaction product in the presence of an appropriate substrate, such as alkaline phosphatase. Alternatively, for example an anti-species and anti-isotype specific third antibody, so coupled to an enzyme, is employed to generate a reaction product that preferably can be detected in a standard spectrophotometric plate reader instrument. For the reaction product development, the washed (as above) antibody-antigen-enzyme complex is preferably exposed to the colorigenic substrate, such as AttoPhos from Roche for about 10 minutes at room temperature, the reaction may be stopped with a low pH buffer such as 50 mM Tris-HCl pH 5.5, or can instead be directly assayed. The amount of specifically bound ZNF216 polypeptide or AKR1C1 polypeptide is for example determined by measurement of the amount of the enzymatic reaction product in each well following excitation at the appropriate wavelength in the spectrophotometer (420 nm in this case). Measurement is preferably made in the plate reader at the emission wavelength (560 nm in this case). Preferably included in the diagnostic is a ZNF216 protein standard or an AKR1C1 protein standard, such as purified recombinant ZNF216 polypeptide or AKR1C1 polypeptide, for example. A dilution series of this protein standard is preferably included in parallel in the ELISA as a control for the reactions and to deduce a protein standard curve for comparison of polypeptide expression levels as is well known in the art. A concentration range corresponding indicative of the particular liver disorder(s) should preferably be provided in the diagnostic. In addition, a comparable fluid or tissue extract should preferably also be included as a control for such ELISA test. This may preferably include serum or plasma from non-diseased individuals and/or serum, plasma or tissue extracts from an appropriate animal model. Such ELISA detection diagnostics are common in the art (see for example, Hauschild et al., 2001, Cancer Res. 158:169-77). The sample: control protein levels determined by ELISA are compared with ELISA-determined disorder specific protein expression ratio values preferably determined in pathologist-confirmed tissues of patients suffering from a disorder according to the invention in relation to control samples. In case the protein level of the sample: control essentially matches the disorder specific protein expression ratio values such matching is preferably indicative of the patient suffering from the disorder. Preferably such diagnosis is carried out for more than 1 polypeptide according to the invention.

[443] In addition the diagnostic may be directed to detecting an endogenous antibody directed against a polypeptide according to the invention, or a functional variant thereof or fragment thereof present in the sample isolated from a patient which antibody or fragment thereof is directed against a polypeptide according to the invention. Detection of such autoimmune antibodies may be accomplished by methods generally known to the skilled artisan, e.g. by immunoaffinity assays such the ELISA

described in detail above using polypeptides according to the invention or functional variants thereof or parts thereof as a probe. The presence of such autoimmune antibodies is indicative of the patient suffering from a disorder according to the invention.

[444] In addition or alternatively, a relevant diagnostic kit based upon immunohistochemical detection of at least one polypeptide according to the invention can be formulated. In such a kit, for example a purified antibody or antibodies specific for the polypeptide(s) according to the invention can be included as well as preferably the reagents necessary to detect the binding of the antibody (ies) to patient cells or tissue sections. These reagents include, for example a specific anti-species and subtype specific secondary antibody -directed against a polypeptide according to the invention of a functional variant thereof- preferably coupled to an enzyme capable of catalysis of e.g. a colorigenic substrate or coupled to a fluorophore (such as Texas Red, for example). Preferably the enzymatic substrate would also be included as well as washing and incubation buffers. An additional optional component of such a kit may be a section of positive control tissue, e.g. liver, or tissues or a section from a packed pellet of cells specifically expressing the polypeptide(s) as a positive tissue control. Instructions provided would include preferred and/or alternative methods of antigen retrieval for detection of the polypeptide(s) according to the invention or e.g., indication that frozen, rather than formalin fixed and paraffin-embedded tissue material should be employed. In this case, recommendations would preferably be included for fixation of frozen tissue sample sections, such as immersion in ice-cold acetone for 10 minutes. Further instructions would preferably provide recommendations for the concentration of antibodies to use in the detection of the gene product(s) as well as e.g., recommended and suggested incubation times and temperatures for exposure of the tissue to the immunological reagents provided. Preferred reaction buffers for the antibody incubations, such as 0.01% - 0.1% tween-20 comprising phosphate buffered saline including 3% normal sheep serum, could also be included. Further, specific conditions for washing of the tissue sections prior to and following incubation in the specific antibody would be preferably included, such as for example, 4 washes with 0.1% tween-20 comprising phosphate buffered saline for 5 minutes each. Such immunohistochemical detection protocols are known to a person skilled in the art. In general the kit would preferably include a panel of images of specific immunohistochemical staining results from positive and negative tissue examples and in particular tables indicating which result is indicative of the patient suffering from the disorder to be diagnosed as a user guide. Utilization of such a kit would preferably rule out, support or confirm diagnoses of the aforementioned liver disorders, liver cancer, or epithelial cancers according to the invention.

[445] As specified above for nucleic acid-based diagnostic approaches, diagnostics based on detection and/or quantitation of polypeptides according to the invention may include 1 or more of such polypeptides. Moreover, simultaneous detection of such polypeptides together with other peptides implicated in the disorders according to the invention may be employed in such diagnostics.

[446] It will be apparent to those skilled in the art that various modifications can be made to the compositions and processes of this invention. Thus, it is intended that the present invention cover such modifications and variations, provided they come within the scope of the appended claims and their equivalents. All publications cited herein are incorporated in their entireties by reference.

[447]

Claims

[001] A diagnostic comprising at least one compound selected from the group consisting of the polypeptide according to SEQ ID 1 to 93, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, and an antibody or an antibody fragment directed against one of the aforementioned polypeptides, combined or together with suitable additives or auxiliaries.

[002] The diagnostic according to claim 1, wherein the nucleic acid is a probe.

[003] The diagnostic according to claim 2, wherein the probe is a DNA probe.

[004] A pharmaceutical composition comprising at least one component selected from the group consisting of the polypeptide according to claim 1, a polypeptide according to SEQ ID 1 to 93, a functional variant of one of the aforementioned polypeptides, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the aforementioned vector, an antibody or a fragment of the antibody directed against one of the aforementioned polypeptides, an antibody or a fragment of the antibody directed against a functional variant of one of the aforementioned polypeptides, a vector comprising a nucleic acid coding for one of the aforementioned antibodies, a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibodies, and a cell comprising the vector comprising a nucleic acid coding for one of the aforementioned antibody fragments, combined or together with suitable additives or auxiliaries.

[005] The pharmaceutical composition according to claim 4, wherein the nucleic acid having a complementary sequence is an antisense molecule or an RNA interference molecule.

[006] A method of diagnosis of a liver disorder or an epithelial cancer, wherein at least one compound selected from the group consisting of a polypeptide according to the sequence of SEQ ID 1 to SEQ ID 93, a functional variant of one of the aforementioned polypeptides, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, an antibody or a fragment of the antibody directed

against one of the aforementioned polypeptides, and an antibody or a fragment of the antibody directed against a functional variant of one of the aforementioned polypeptides, is identified in the sample of a patient and compared with at least one compound of a reference library or of a reference sample.

[007] The method according to claim 6, wherein the liver disorder, is a disorder selected from the group consisting of cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's Disease, haemochromatosis, hepatocellular carcinoma, benign liver neoplasms, and focal nodular hyperplasia.

[008] The method according to claim 6, wherein the epithelial cancer is an adeno-carcinoma of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[009] A method of treating a patient suffering from a liver disorder or an epithelial cancer, wherein at least one component selected from the group consisting of a polypeptide according SEQ ID 1 to 93, a functional variant of one of the afore-mentioned polypeptides, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the afore-mentioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, a cell comprising the aforementioned vector, an antibody or a fragment of the antibody directed against one of the aforementioned polypeptides, an antibody or a fragment of the antibody directed against a functional variant of one of the afore-mentioned polypeptides, a vector comprising a nucleic acid coding for the antibody, a cell comprising the vector comprising a nucleic acid coding for the antibody, and a cell comprising the vector comprising a nucleic acid coding for the antibody fragment, combined or together with suitable additives or auxiliaries, is administered to the patient in need of a the treatment in a thera-peutically effective amount.

[010] The method of treating according to claim 9, wherein the nucleic acid having a complementary sequence is an antisense molecule or an RNA interference molecule.

[011] The method of treating according to claim 10, wherein the RNA interference molecule is administered in the form of a double stranded RNA or a vector expressing the double stranded RNA.

[012] The method according to claim 10, wherein the RNA interference molecule has a size range selected from the group consisting of from 15 to 30 nucleotides.

[013] The method according to one of claims 9 to 12, wherein the liver disorder, is a

disorder selected from the group consisting of cirrhosis, alcoholic liver disease, chronic hepatitis, Wilson's Disease, haemochromatosis, hepatocellular carcinoma, benign liver neoplasms, and focal nodular hyperplasia.

[014] The method according to one of claims 9 to 13, wherein the epithelial cancer is an adenocarcinoma of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[015] A method of stimulating an immune response to a polypeptide according to the sequence of SEQ ID 1 to SEQ ID 93, or a functional variant thereof in a patient suffering from a liver disorder or an epithelial cancer, wherein at least one component selected from the group consisting of a polypeptide according to the sequence of SEQ ID 1 to SEQ ID 93 , a functional variant thereof, a nucleic acid encoding one of the aforementioned polypeptides, a variant of one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, a cell comprising one of the aforementioned nucleic acids, and a cell comprising the aforementioned vector, is administered to the patient in need of such treatment in an amount effective to stimulate the immune response in the patient.

[016] A method for identifying at least one nucleic acid according to SEQ ID 94 to SEQ ID 186, or a variant thereof differentially expressed in a sample isolated from a patient relative to a reference library or a reference sample comprising the following steps: (a) detecting the expression of at least one nucleic acid according to SEQ ID 94 to SEQ ID 186, or a variant thereof in a sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of the said nucleic acid(s) in a reference library or in a reference sample, (c) identifying said nucleic acid(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample.

[017] A method of diagnosing a liver disorder or an epithelial cancer comprising the following steps: (a) detecting the expression of at least one nucleic acid according to SEQ ID 94 to SEQ ID 186, or a variant thereof in a sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of said nucleic acid(s) in a reference library or in a reference sample, (c) identifying said(s) nucleic acid which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample, and (d) matching said nucleic acid(s) identified in step (c) to said nucleic acid(s) differentially expressed in a pathologic reference sample or pathologic reference library, wherein the matched nucleic acid(s) is (are) indicative of the patient suffering from a liver disorder or an

epithelial cancer.

[018] The method according to claim 17, wherein in step (a) at least 2 nucleic acids are identified.

[019] The method according to claim 17, wherein in step (a) the detection of said nucleic acid(s) is (are) by PCR based detection or by a hybridization assay.

[020] The method according to one of claims 17 to 19, wherein in step (b) the expression of said nucleic acid(s) is compared by a method selected from the group consisting of solid-phase based screening methods, hybridization, subtractive hybridization, differential display, and RNase protection assay.

[021] The method according to one of claims 17 to 20, wherein the sample isolated from the patient is selected from the group consisting of liver tissue, a liver cell, tissue from another organ subject to cancerous transformation, a cell from this organ, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[022] The method according to one of claims 17 to 21, wherein the reference sampleis isolated from a source selected from a non-diseased sample of the same patient and a non-diseased sample from another subject.

[023] The method according to one of claims 17 to 22, wherein the reference sampleis selected from the group consisting of liver tissue, a liver cell, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[024] The method according to one of claims 17 to 23, wherein the reference libraryis an expression library or a data base comprising clones or data on liver disorder-specific expression of said nucleic acid(s) of step (a).

[025] The method according to one of claims 17 to 24, wherein the pathologic reference sample is isolated from a source selected from a diseased sample from another patient suffering from a liver disorder or epithelial cancer.

[026] The method according to claim 17 to 25, wherein the pathologic reference library is a data base comprising data on differential expression of said nucleic acid(s) in step (a) in samples isolated from another patient suffering from a liver disorder or epithelial cancer relative to control expression in a reference sample or reference library.

[027] The method according to claim 17 to 26, wherein the liver disorder, is a disorder selected from the group consisting of hepatocellular carcinoma, benign liver neoplasms, and cirrhosis.

[028] The method according to claim 17 to 26, wherein the epithelial cancer is an adenocarcinoma of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin and the breast.

[029] A method for identifying at least one polypeptide according to SEQ ID 1 to SEQ ID 93, or a functional variant thereof differentially expressed in a sample isolated from a patient relative to a reference library or a reference sample comprising the following steps: (a) detecting the expression of at least one polypeptide accord ing to SEQ ID 1 to SEQ ID 93, or a functional variant thereof in a sample isolated from a patient, (b) comparing the expression of said polypeptide(s) detected in step (a) with the expression of said polypeptide(s) in a reference library or in a reference sample, (c) identifying said polypeptide(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample.

[030] A method of diagnosing a liver disorder or epithelial cancers comprising the following steps: (a) detecting the expression of at least one polypeptide according to SEQ ID 1 to SEQ ID 93, or functional variants thereof in a sample isolated from a patient, (b) comparing the expression of said polypeptide(s) detected in step (a) with the expression of said polypeptide(s) in a reference library or in a reference sample, (c) identifying said polypeptide(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample, and (d) matching said polypeptide(s) identified in step (c) with said polypeptide(s) differentially expressed in a pathologic reference sample or pathologic reference library, wherein the matched polypeptide(s) are indicative of the patient suffering from a liver disorder, or an epithelial cancer.

[031] The method according to claim 30, wherein at least 2 polypeptides are identified.

[032] The method according to claim 30 or 31, wherein the polypeptides are detected by a method selected from the group consisting of gel electrophoresis, chromatographic techniques, immunoblot analysis, immunohistochemistry, enzyme based immunoassay, surface plasmon resonance, HPLC, mass spectroscopy, immunohistochemistry, and enzyme based immunoassay.

[033] The method according to one of claims 30 to 32, wherein the polypeptides are compared by a method selected from the group consisting of two dimensional gel electrophoresis, chromatographic separation techniques, immunoblot analysis, surface plasmon resonance, immunohistochemistry, and enzyme based immunoassay.

[034] The method according to one of claims 30 to 33, wherein the sample isolated from a patient is selected from the group consisting of liver tissue, a liver cell, tissue from another organ subject to cancerous transformation, a cell from this organ, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[035] The method according to one of claims 30 to 34, wherein the reference sampleis isolated is from a source selected from a non-diseased sample of the same patient and a non-diseased sample from another subject.

[036] The method according to one of claims 30 to 35 wherein the reference sample is selected from the group consisting of liver tissue, a liver cell, blood, serum, plasma, ascitic fluid, pleural effusion, cerebral spinal fluid, saliva, urine, semen, and feces.

[037] The method according to one of claims 30 to 36, wherein the reference libraryis an expression library or a data base comprising clones or data on liver disorder-specific expression of said polypeptide(s) of step (a).

[038] The method according to claim 30 to 37, wherein the pathologic reference sample is isolated from a source selected from a diseased sample from another patient suffering from a liver disorder and epithelial cancer.

[039] The method according to claim 30 to 38, wherein the pathologic reference library is a data base comprising data on differential expression of said polypeptide(s) of step (a) in samples isolated from another patient, suffering from a liver disorder or epithelial cancer, relative to control expression in a reference sample or reference library.

[040] The method according to claim 30 to 39, wherein the liver disorders is a disorder selected from the group consisting of hepatocellular carcinoma, benign liver neoplasms, and cirrhosis.

[041] The method according to one of claims 30 to 40, wherein the epithelial cancer is an adenocarcinoma of an organ selected from the group consisting of the lung, the stomach, the kidney, the colon, the prostate, the skin, and the breast.

[042] A method of preventing a patient from developing a liver disorder or an epithelial cancer, wherein at least one component selected from the group consisting of a polypeptide according to the sequence of SEQ ID 1 to SEQ ID 93, a functional variant thereof, a nucleic acid encoding one of the afore-mentioned polypeptides, a variant of one of the aforementioned nucleic acids, a nucleic acid having a sequence complementary to one of the aforementioned nucleic acids, a nucleic acid which is a non-functional mutant variant of one of the aforementioned nucleic acids, a vector comprising one of the aforementioned nucleic acids, or a variant thereof, a cell comprising one of the aforementioned nucleic acids, or a variant thereof, and a cell comprising the aforementioned vector, is administered to the patient in need of such preventive treatment in a therapeutically effective amount.

[043] A method of identifying a pharmacologically active compound comprising the following steps: (a) providing at least one polypeptide according to the SEQ ID 1

to 93, or a functional variant thereof, (b) contacting said polypeptide(s) with (a) compound(s) suspected to be pharmacologically active , (c) assaying the interaction of said polypeptide(s) of step (a) with said compound(s) suspected to be pharmacologically active, (d) identifying said compound(s) suspected to be pharmacologically active which directly or indirectly interact with said polypeptide(s) of step (a).

[044] The method according to claim 43, wherein said polypeptide(s) of step (a) is (are) attached to a column, said polypeptide(s) is (are) attached to an array, contained in an electrophoresis gel, attached to a membrane, or is (are) expressed by a cell.

[045] The method according to claim 43 or 44, wherein the interaction is assayed enzyme or fluorescence based cellular reporter methods.

[046] The method according to claim 43 or 44, wherein the interaction is assayed by surface plasmon resonance, HPLC, or mass spectroscopy.

[047] The method according to claim 43, wherein the direct or indirect functional interaction of step (d) is selected from the group consisting of induction of the expression of said polypeptide(s) of step (a), inhibition of said polypeptide(s), activation of the function of said polypeptide(s), and inhibition of the function of said polypeptide(s).

[048] An isolated polypeptide comprising a sequence according to SEQ ID 32, or a functional variant thereof.

[049] A fusion protein comprising a polypeptide according to claim 48.

[050] An isolated nucleic acid, or a variant thereof encoding the polypeptide according to claim 48.

[051] The nucleic acid according to claim 50, wherein the nucleic acid is a single-stranded or double-stranded RNA.

[052] The nucleic acid according to claim 50, wherein the nucleic acid comprises a nucleic acid according to SEQ ID 125.

[053] A vector comprising a nucleic acid according to claim 50.

[054] The vector according to claim 53, wherein the vector is selected from the group consisting of a knock-out gene construct, a plasmid, a shuttle vector, a phagemid, a cosmid, a viral vector, and an expression vector.

[055] A cell comprising the nucleic acid according to claim 50.

[056] A cell comprising the vector according to claim 53.

[057] The cell according to claim 56, wherein the cell is a transgenic embryonic non-human stem cell.

[058] A transgenic non-human mammal comprising the nucleic acid according to claim 50.

[059] An antibody or an antibody fragment thereof, wherein the antibody is directed against the polypeptide according to claim 48 or against the nucleic acid according to claim 50.

[060] A nucleic acid which comprises a nucleic acid having a sequence complementary to the nucleic acid according to claim 50 or a non-functional mutant variant of the nucleic acid according to claim 50.

[061] The nucleic acid according to claim 60, wherein the nucleic acid having a complementary sequence is an antisense molecule or an RNA interference molecule.

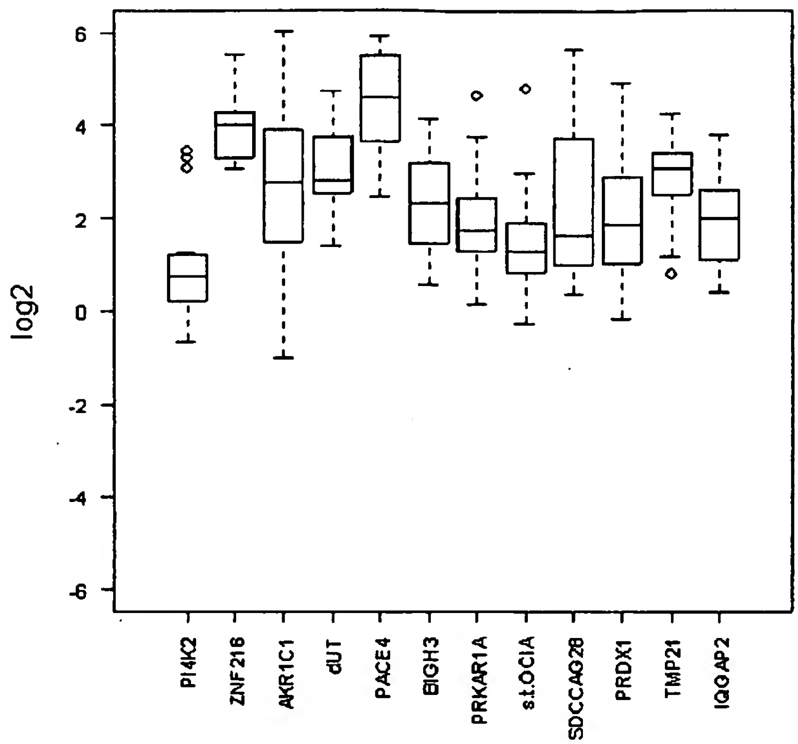
[062] A vector comprising the nucleic acid according to claim 60.

[063] The vector according to claim 62, wherein the vector is selected from the group consisting of a plasmid, a shuttle vector, a phagemid, a cosmid, a viral vector, and an expression vector.

[064] A cell comprising the nucleic acid according to claim 62.

[065] A cell comprising the vector according to claim 64.

[Fig. 001]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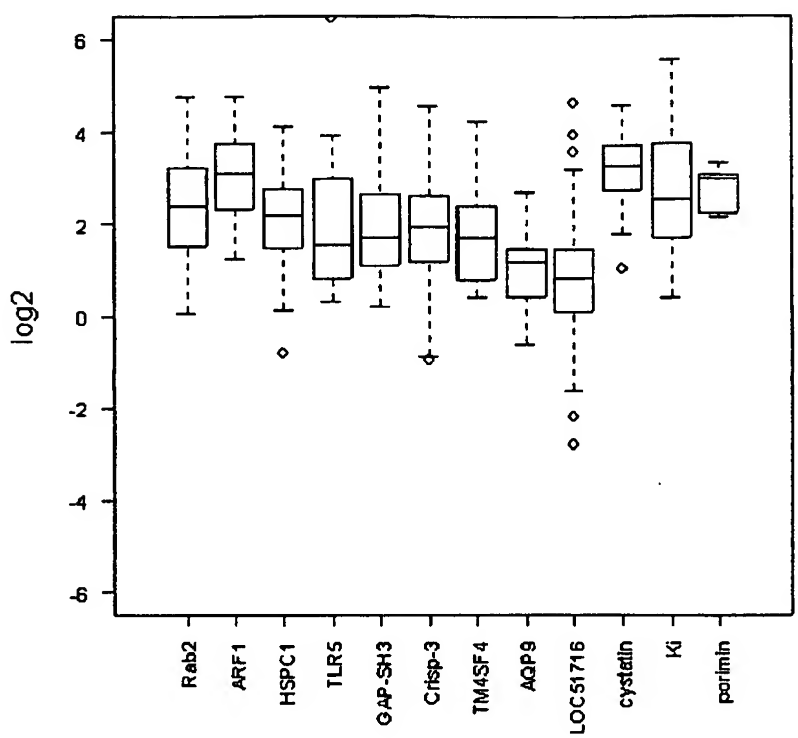
[Fig. 002]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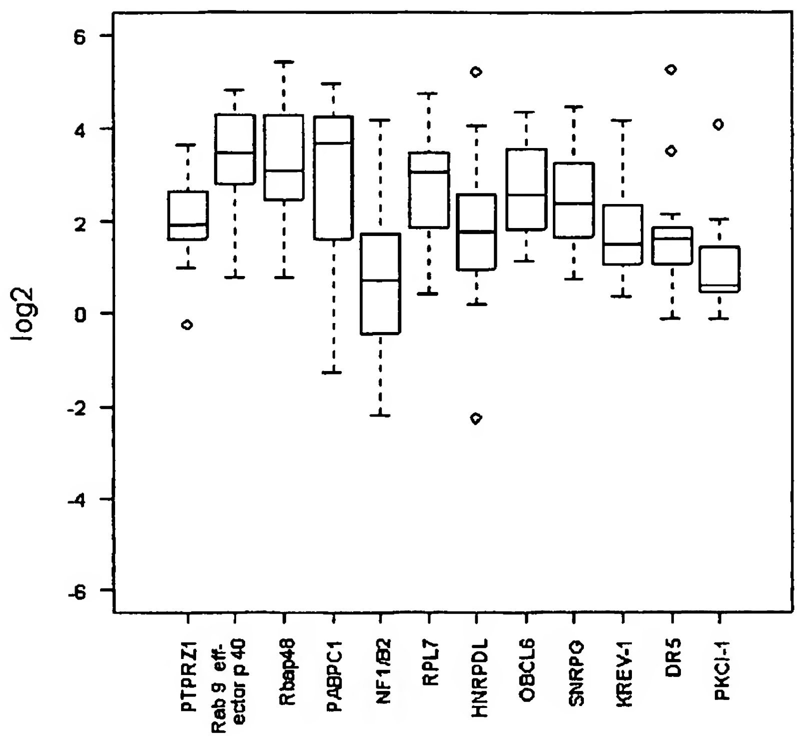
[Fig. 003]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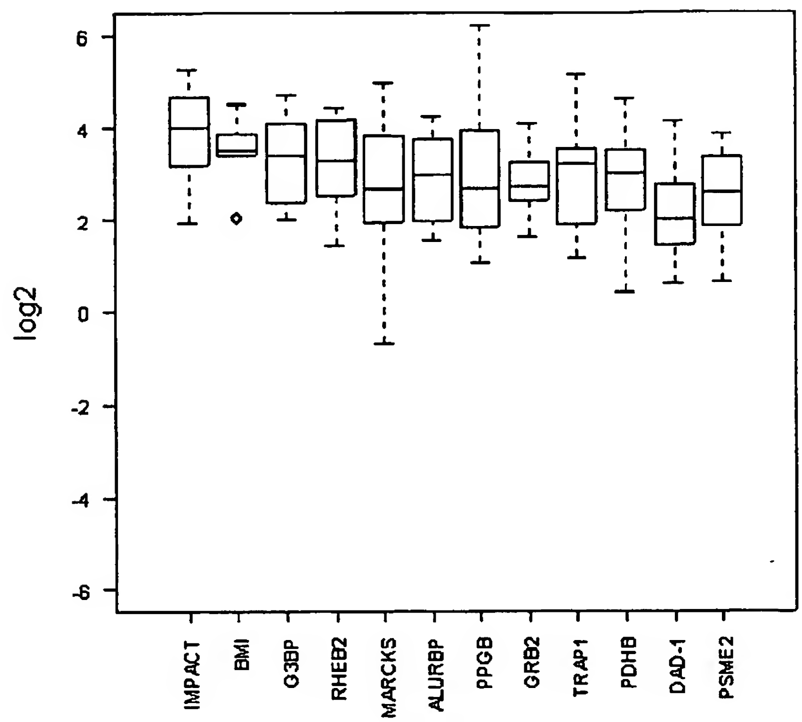
[Fig. 004]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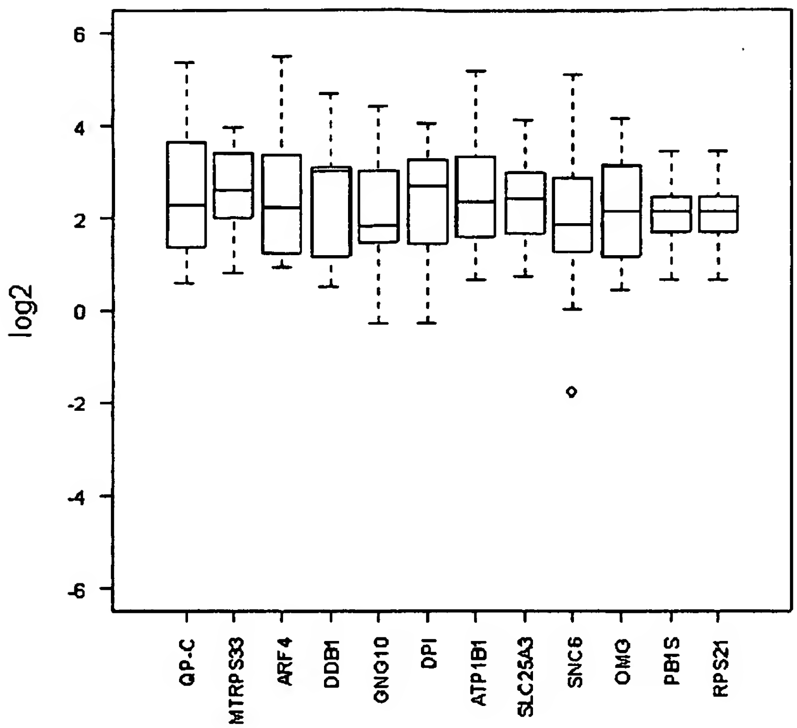
[Fig. 005]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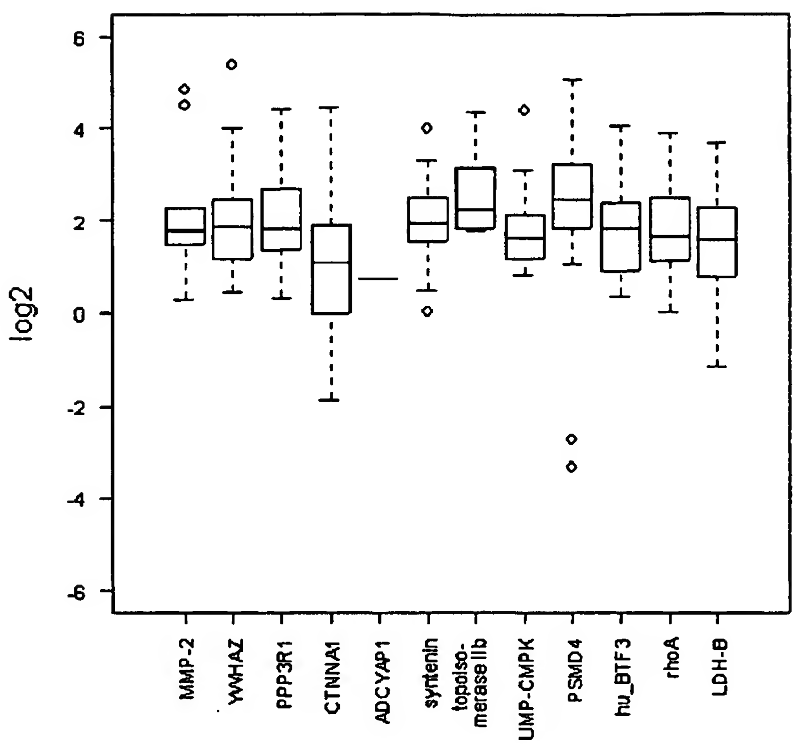
[Fig. 006]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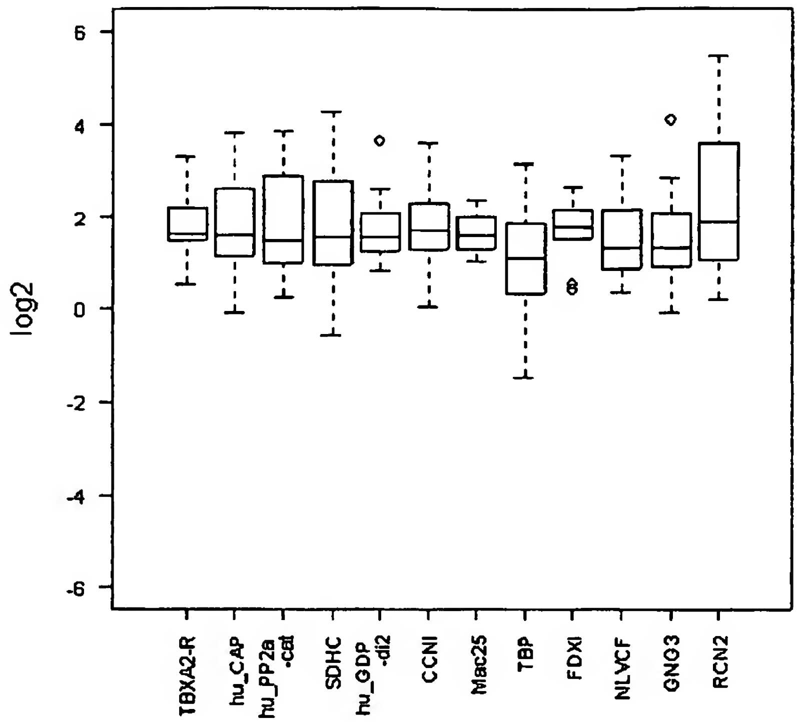
[Fig. 007]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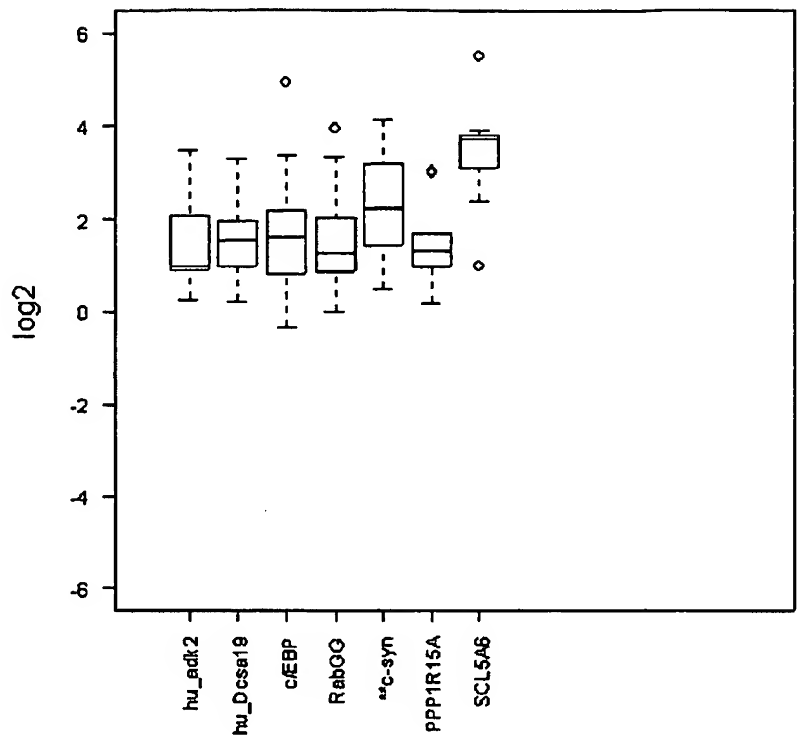
[Fig. 008]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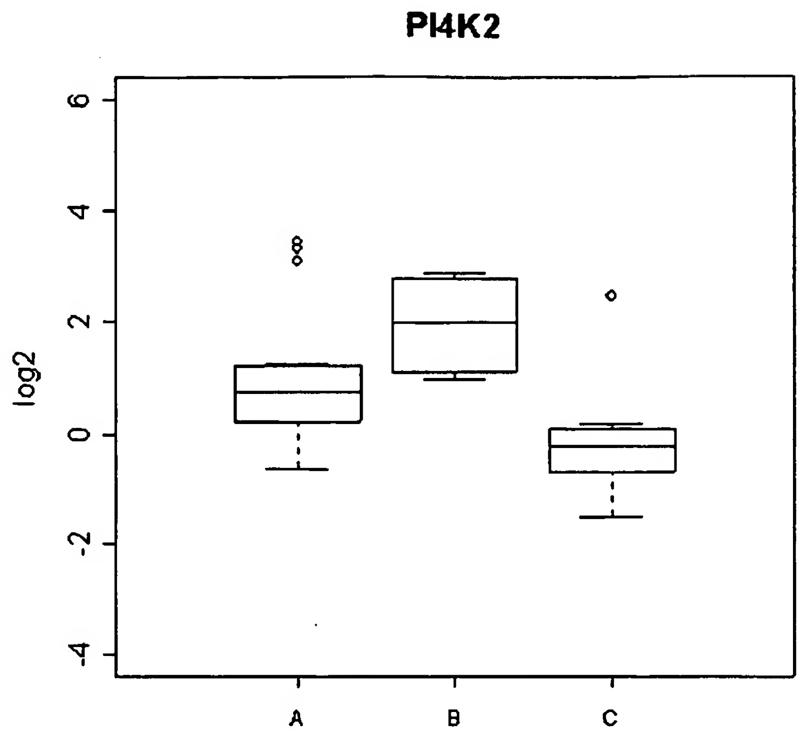
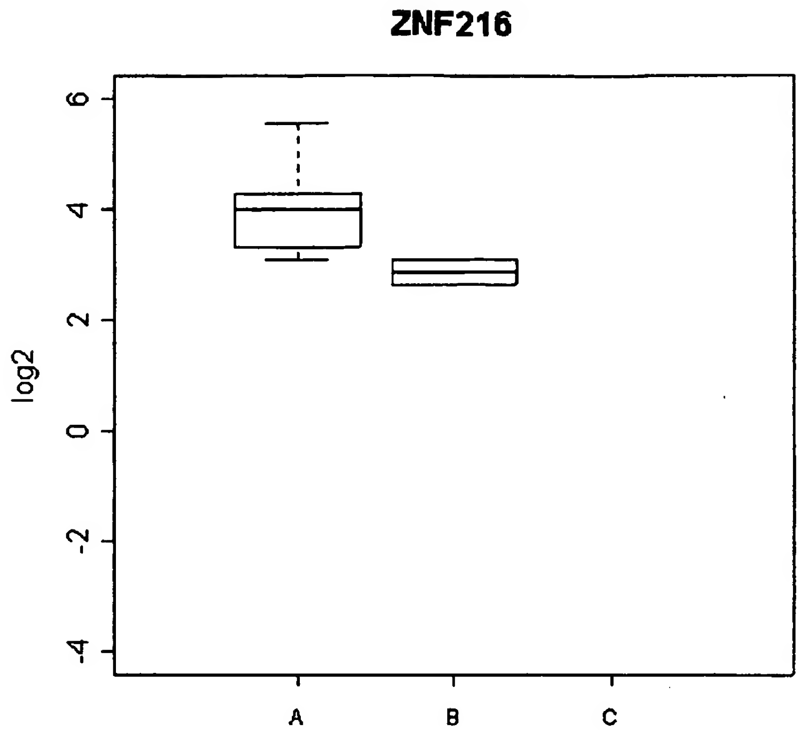
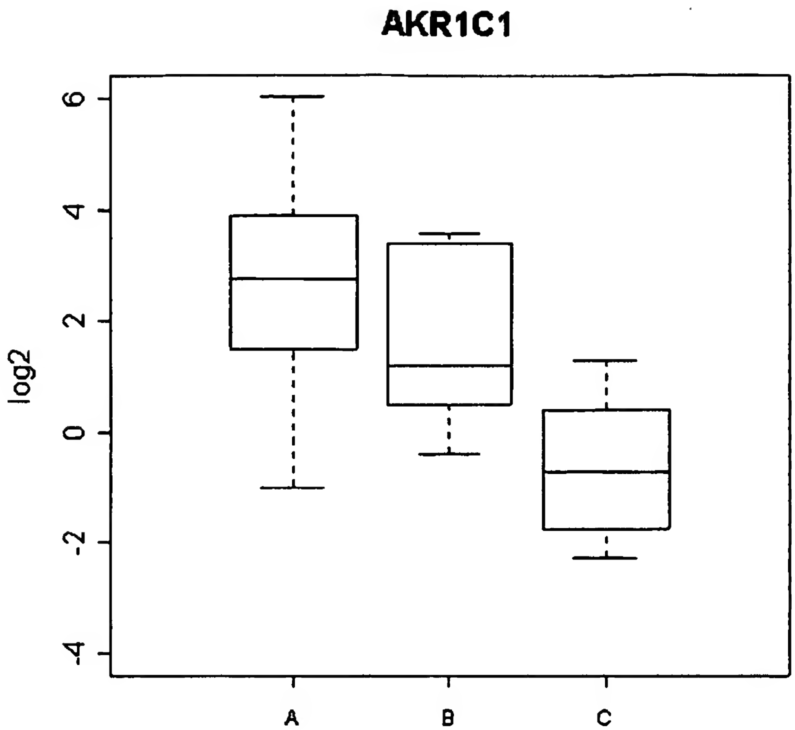
[Fig. 009]



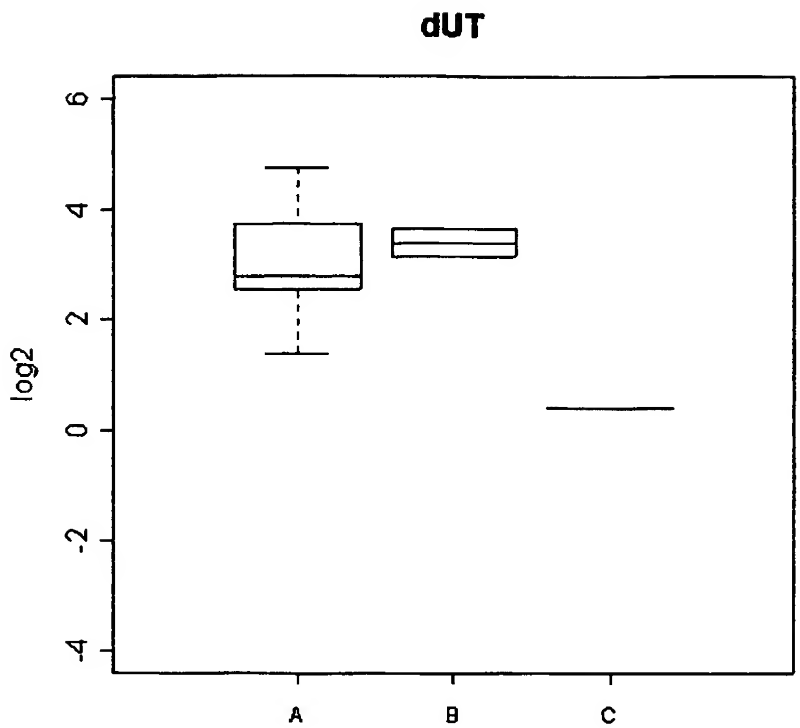
[Fig. 010]



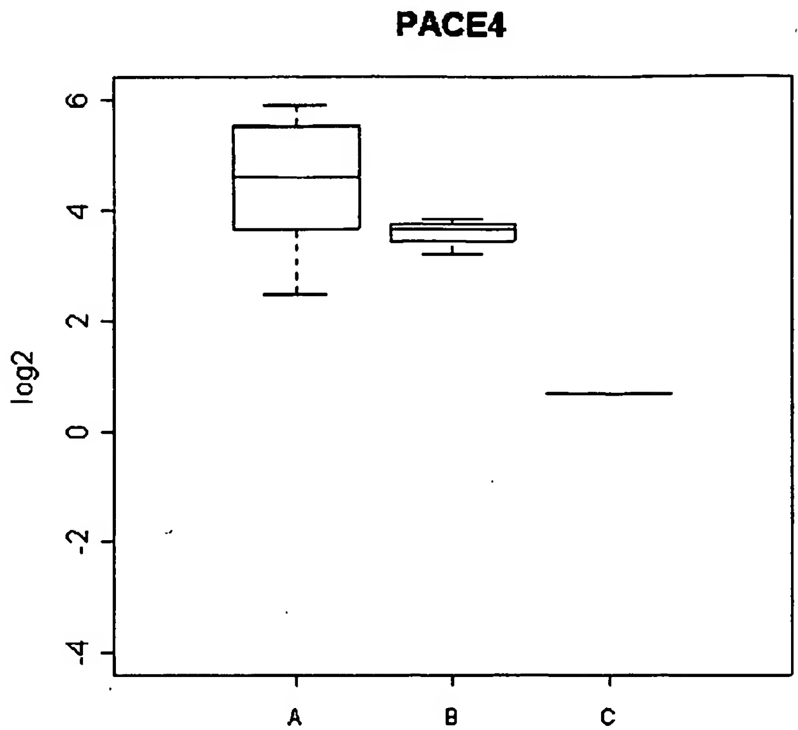
[Fig. 011]



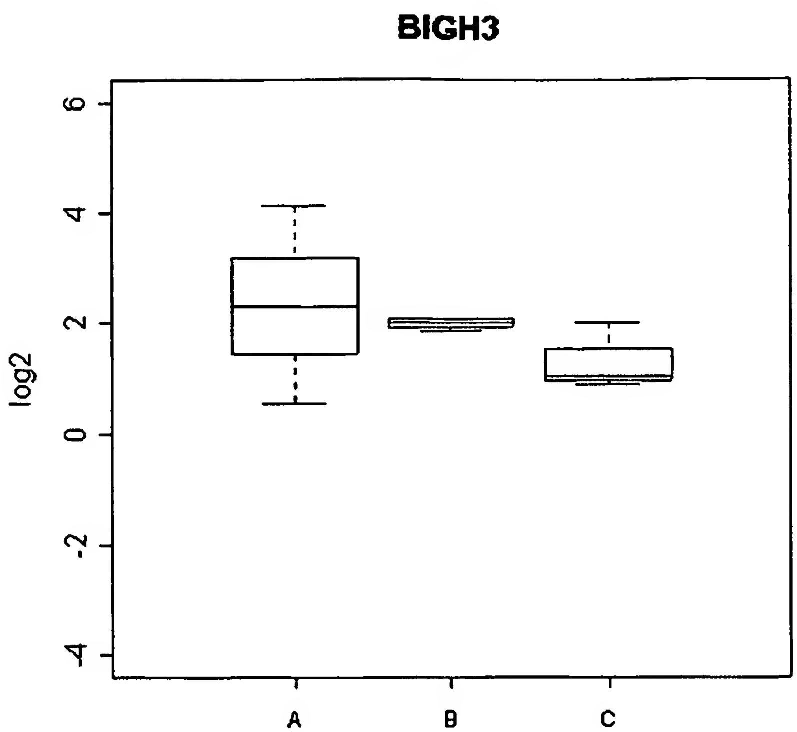
[Fig. 012]



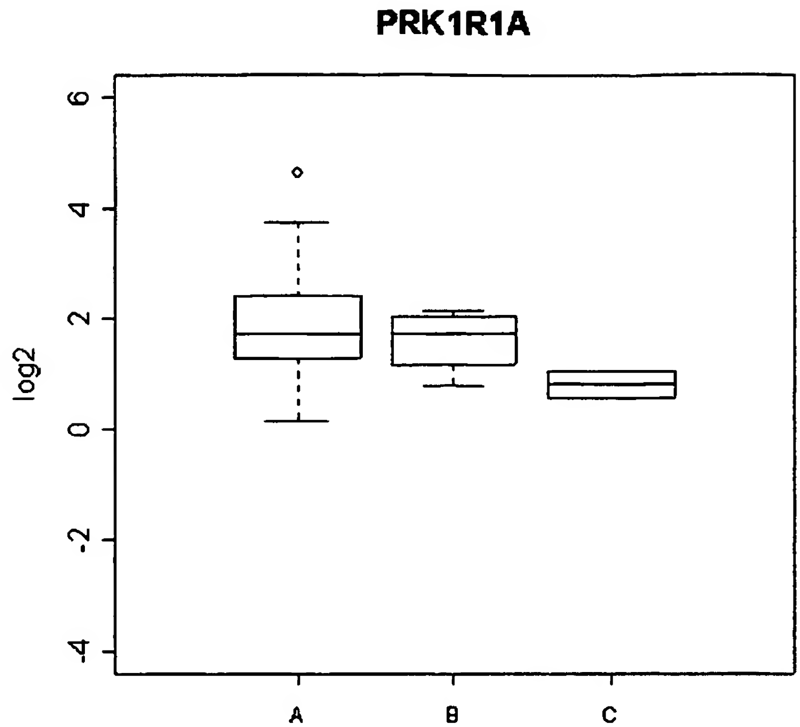
[Fig. 013]



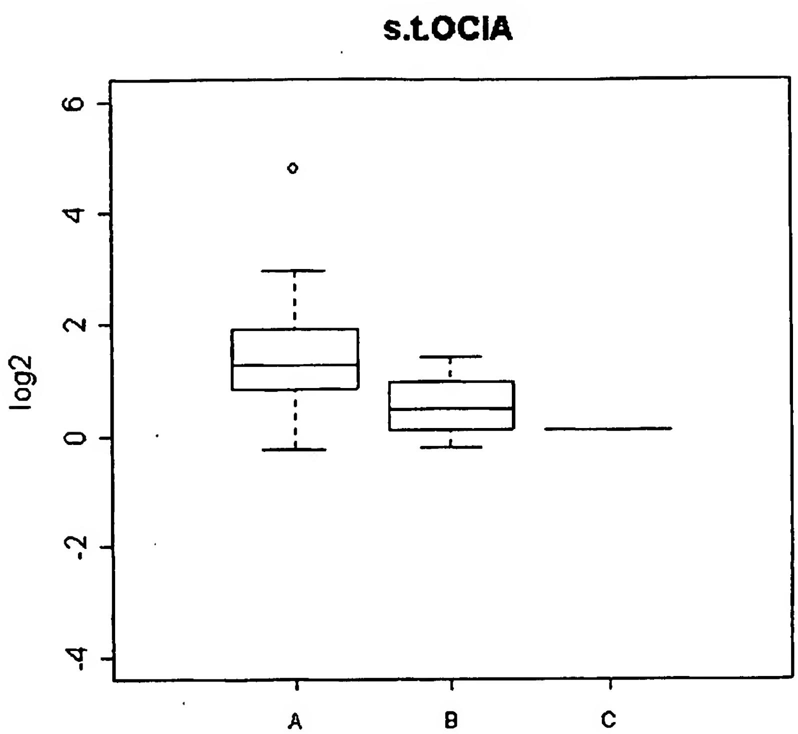
[Fig. 014]



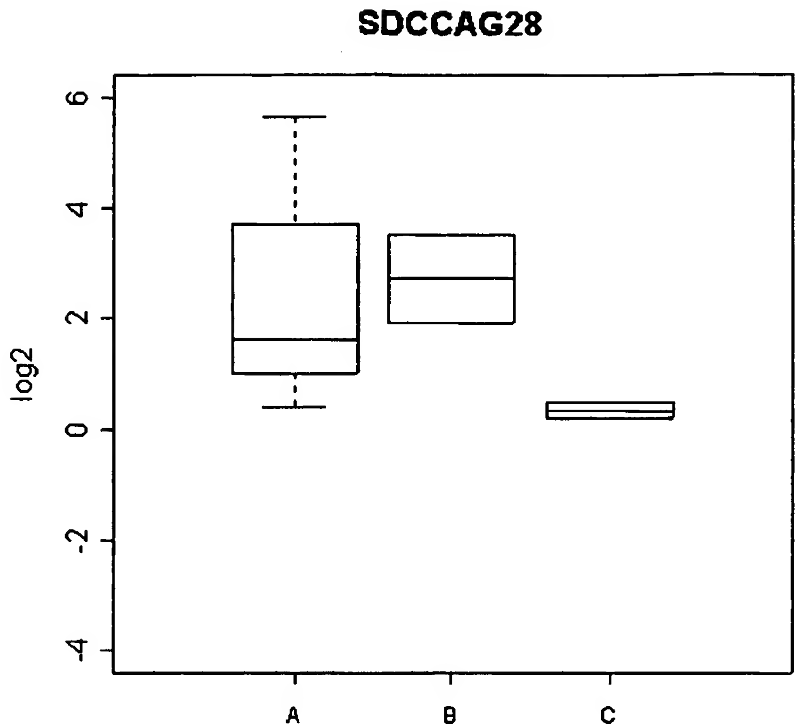
[Fig. 015]



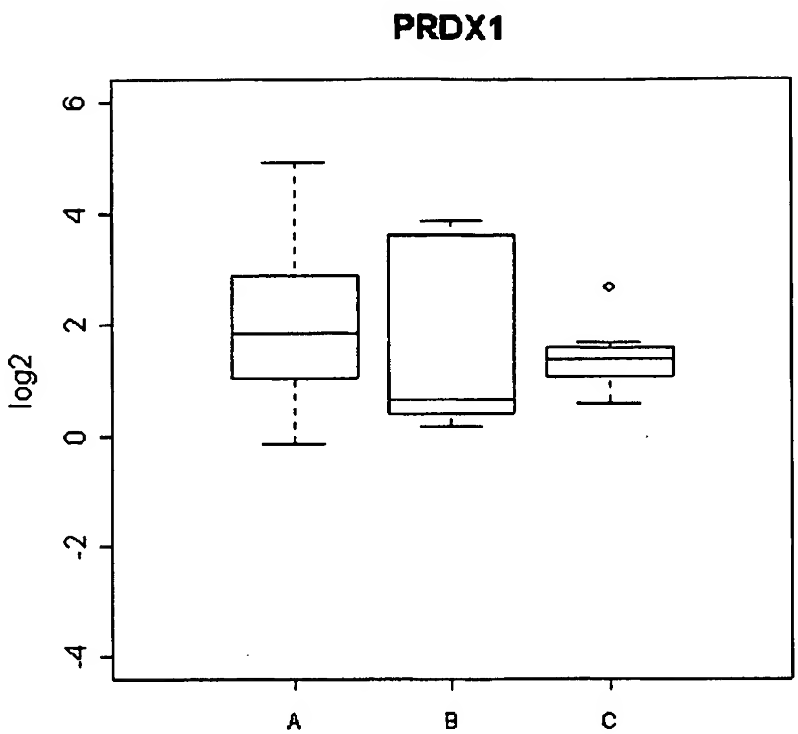
[Fig. 016]



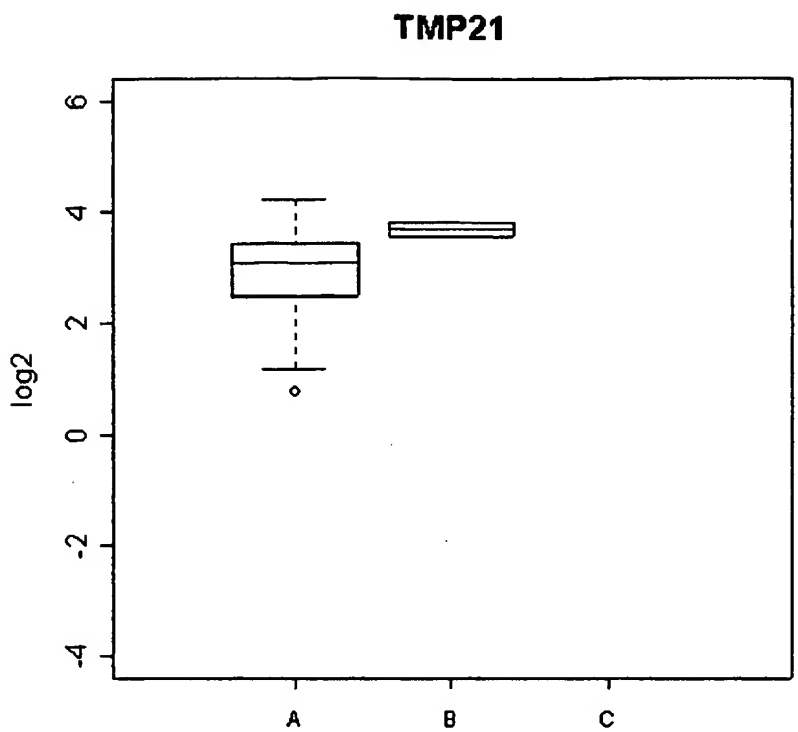
[Fig. 017]



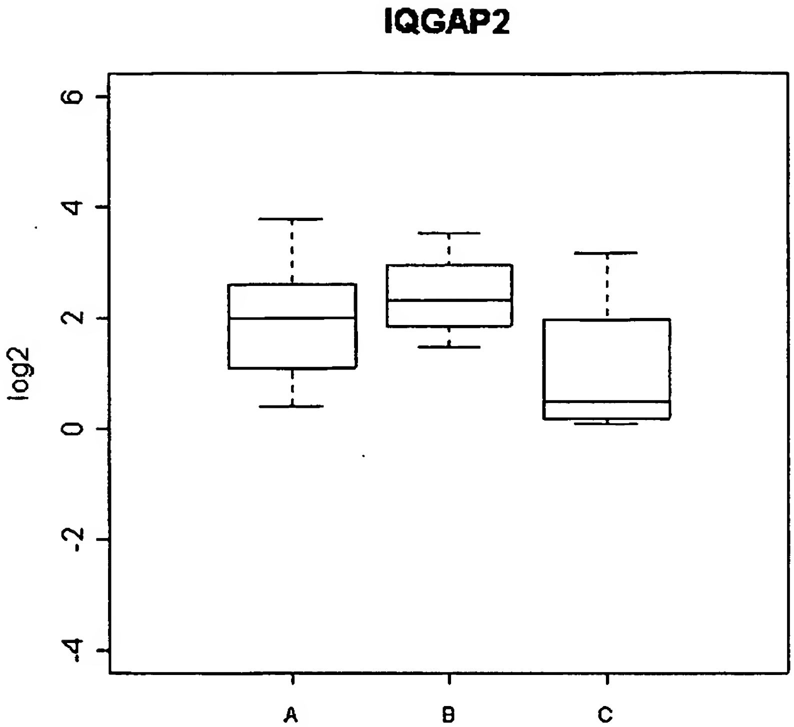
[Fig. 018]



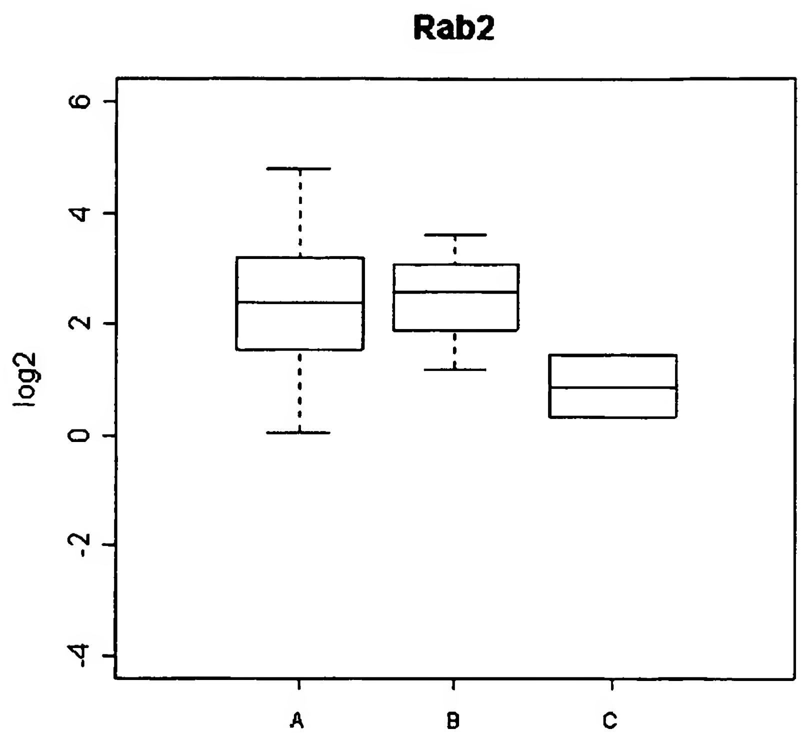
[Fig. 019]



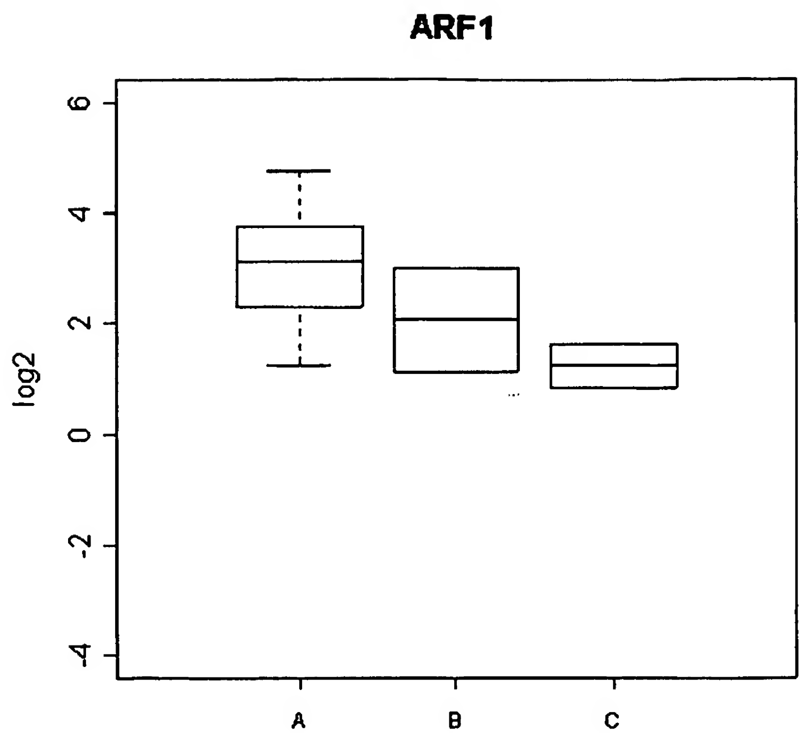
[Fig. 020]



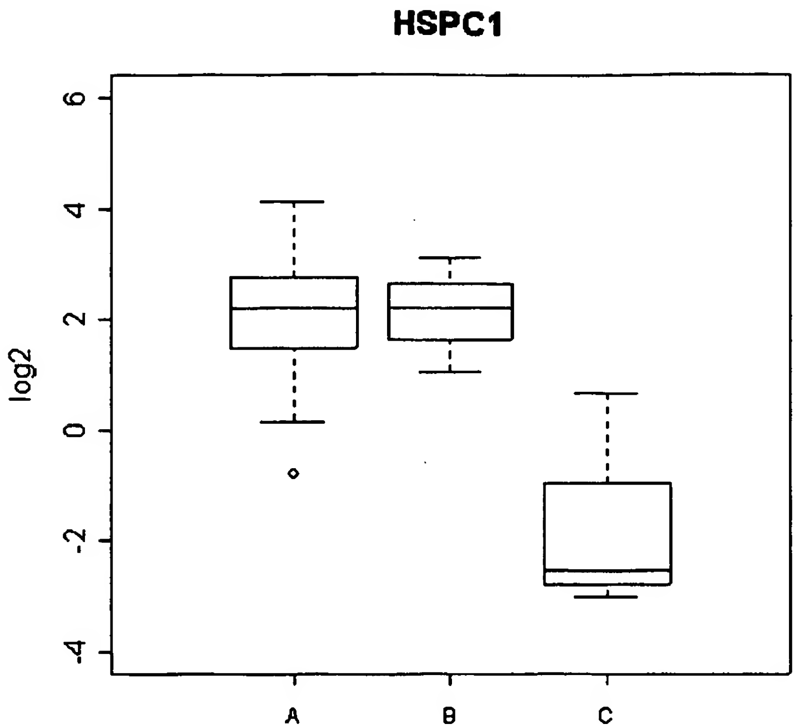
[Fig. 021]



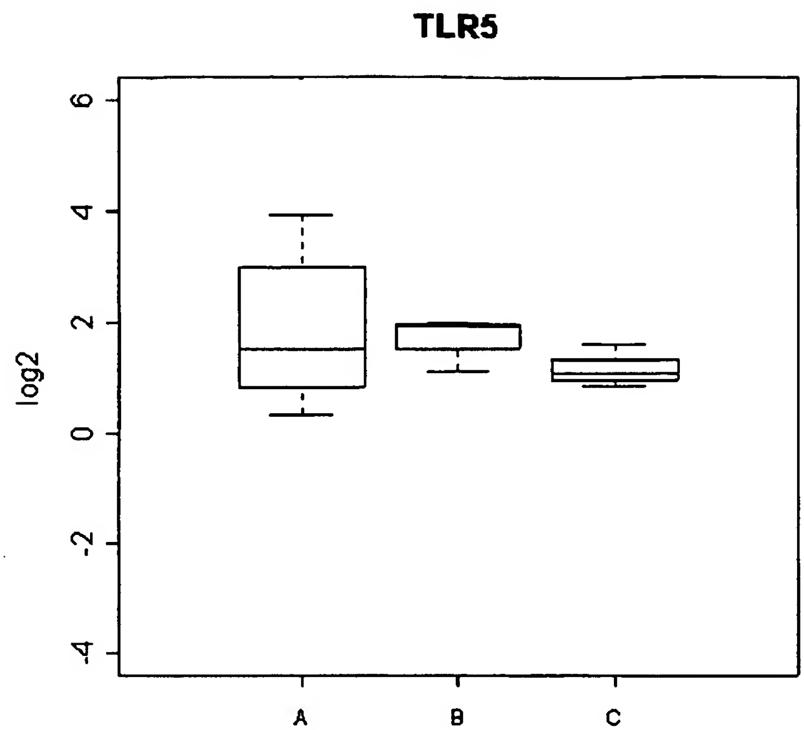
[Fig. 022]



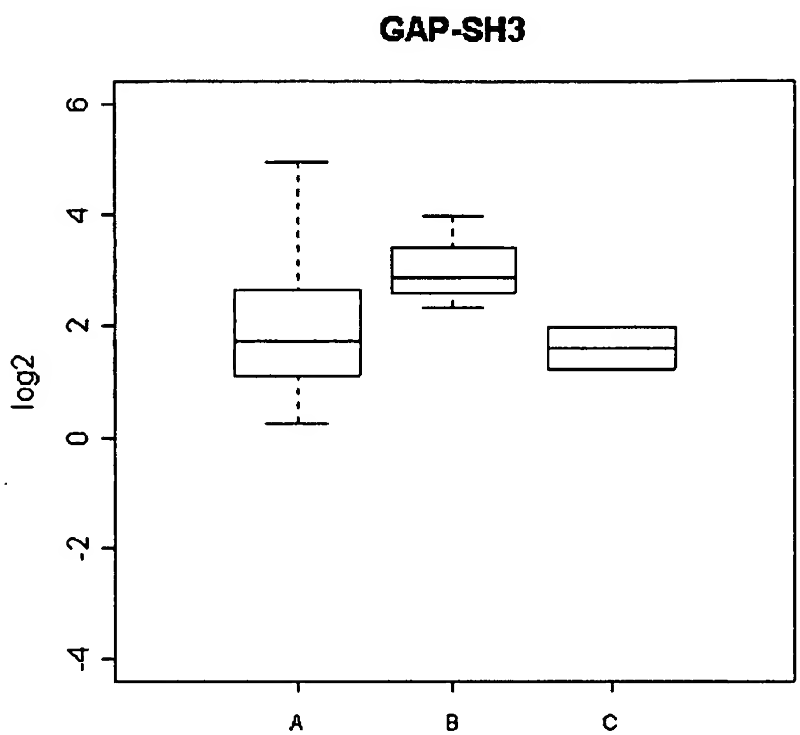
[Fig. 023]



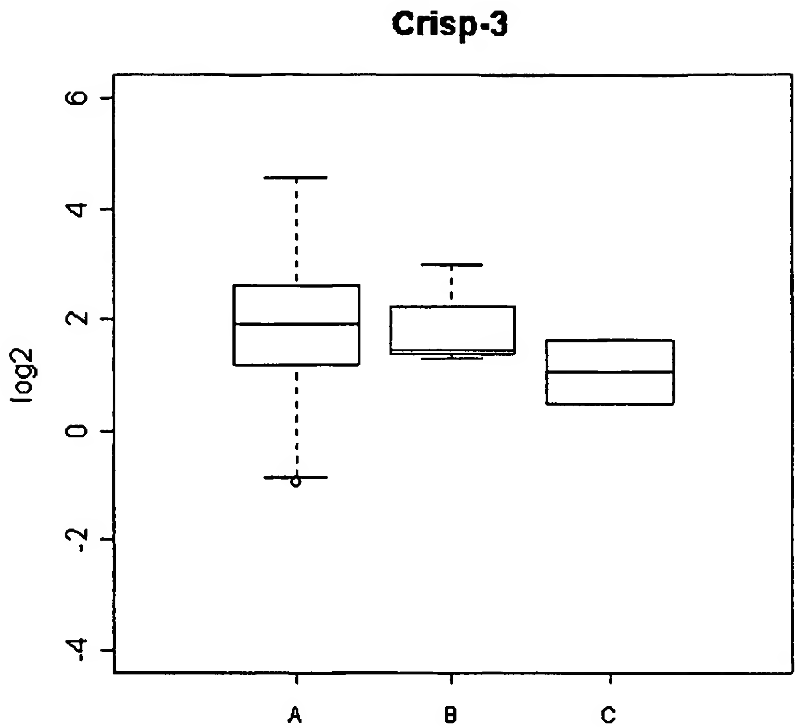
[Fig. 024]



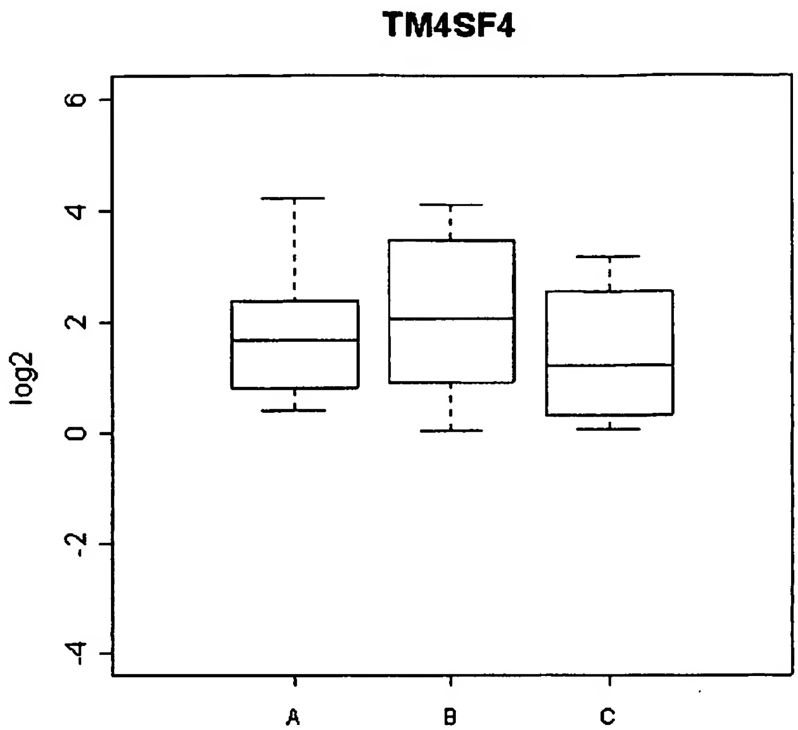
[Fig. 025]



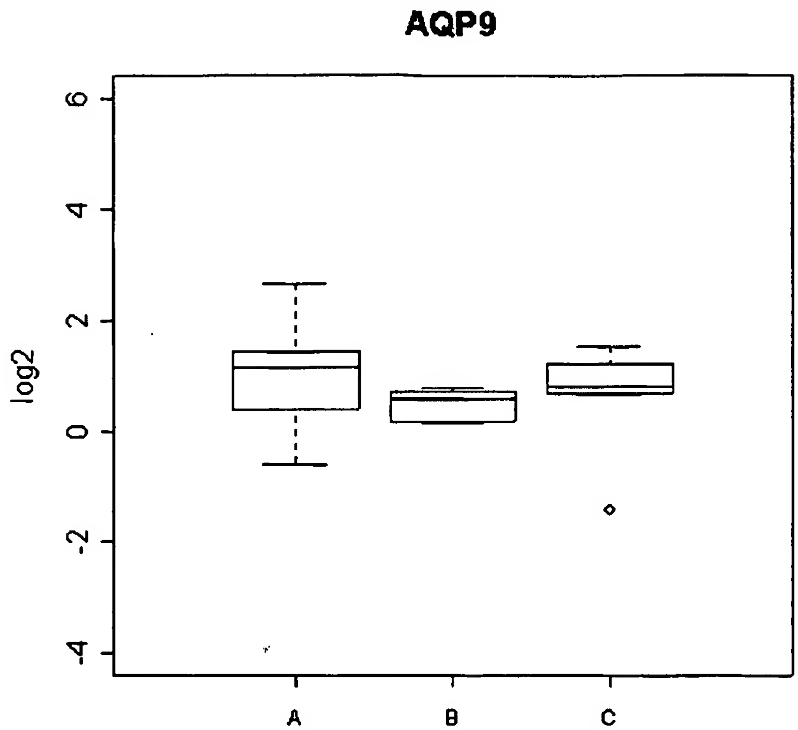
[Fig. 026]



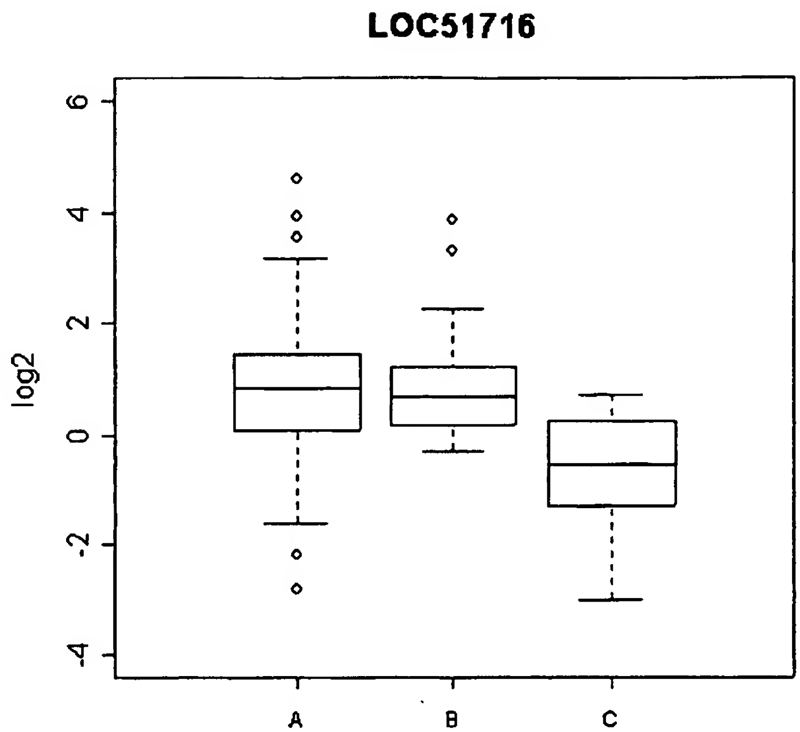
[Fig. 027]



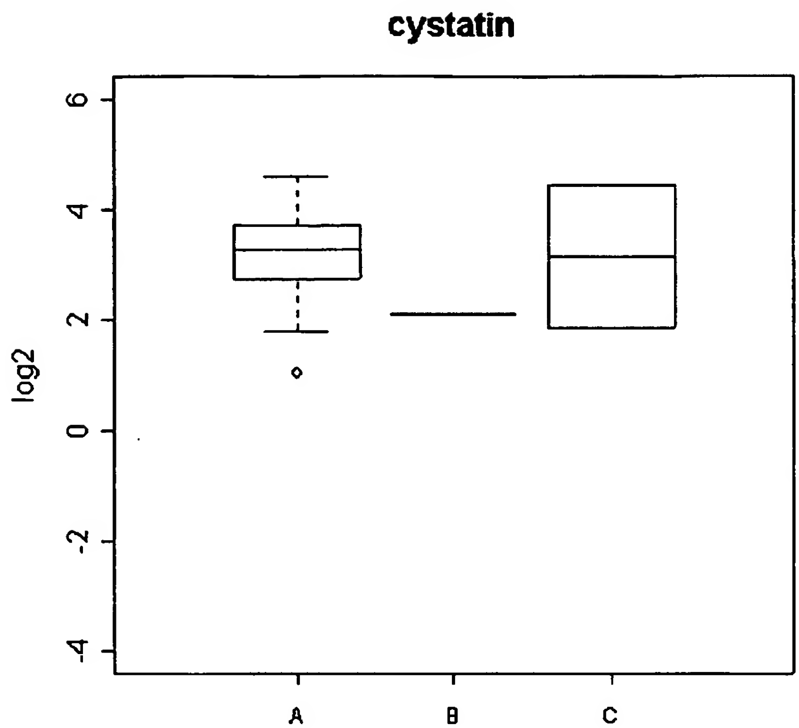
[Fig. 028]



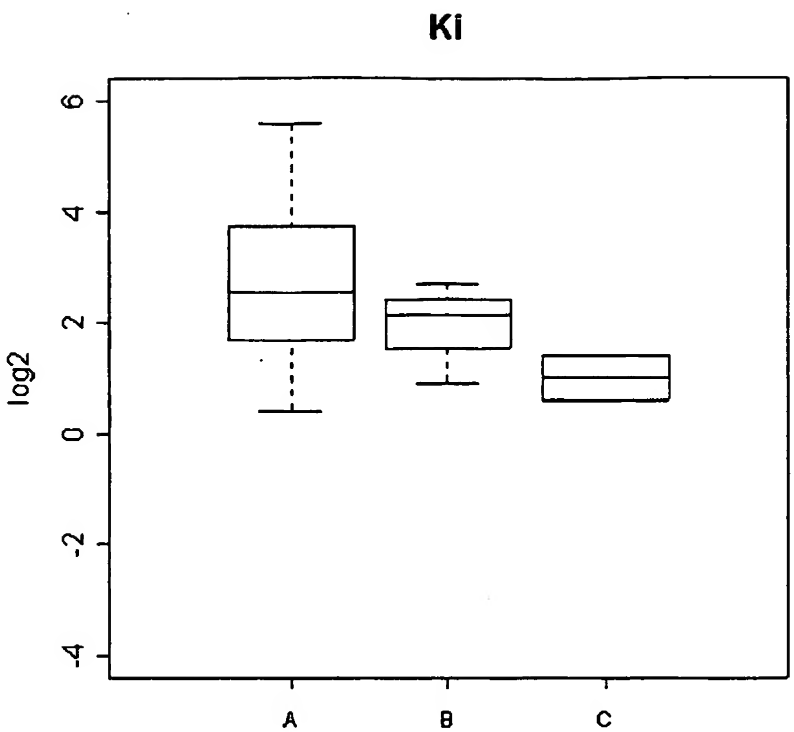
[Fig. 029]



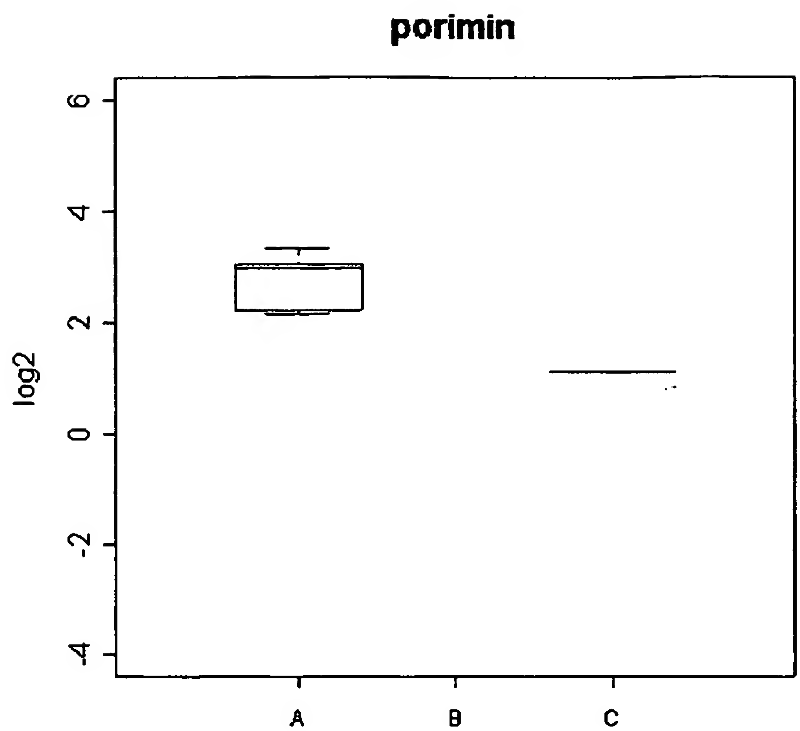
[Fig. 030]



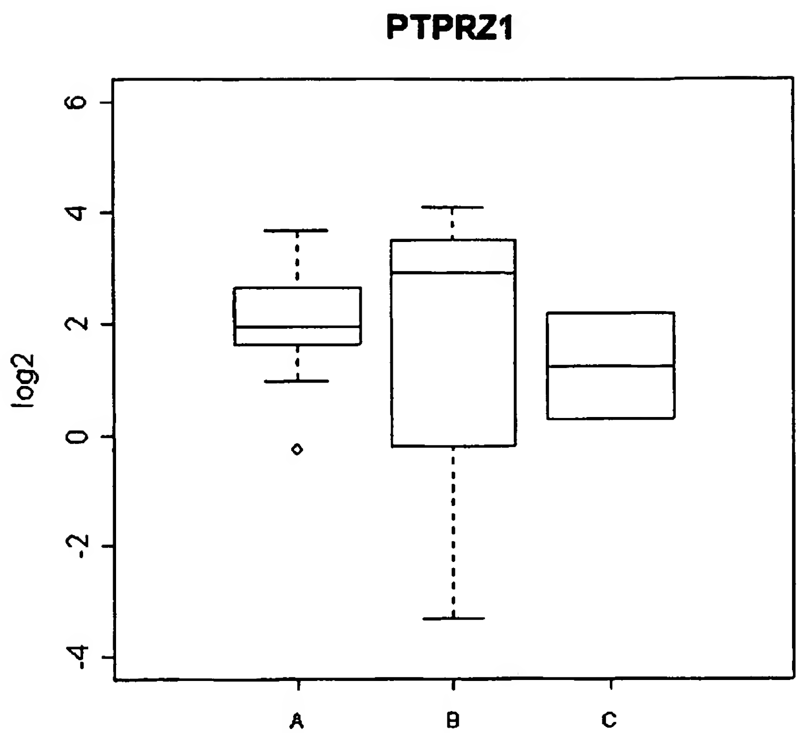
[Fig. 031]



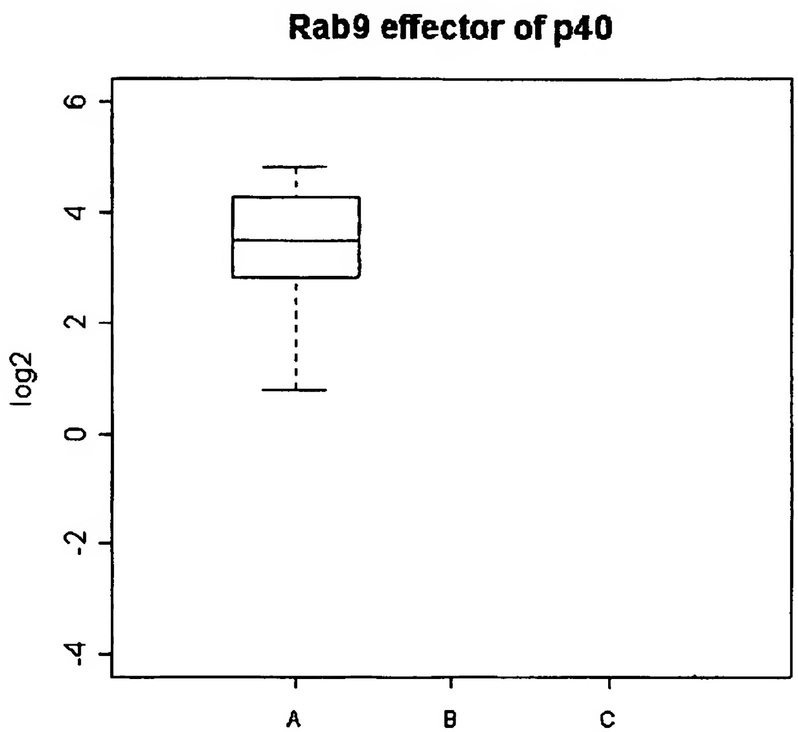
[Fig. 032]



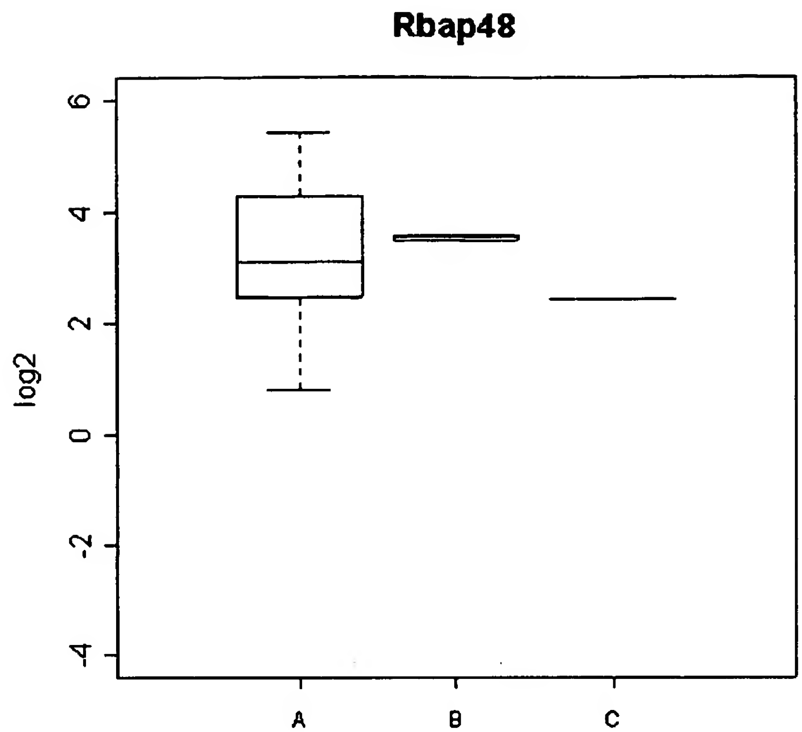
[Fig. 033]



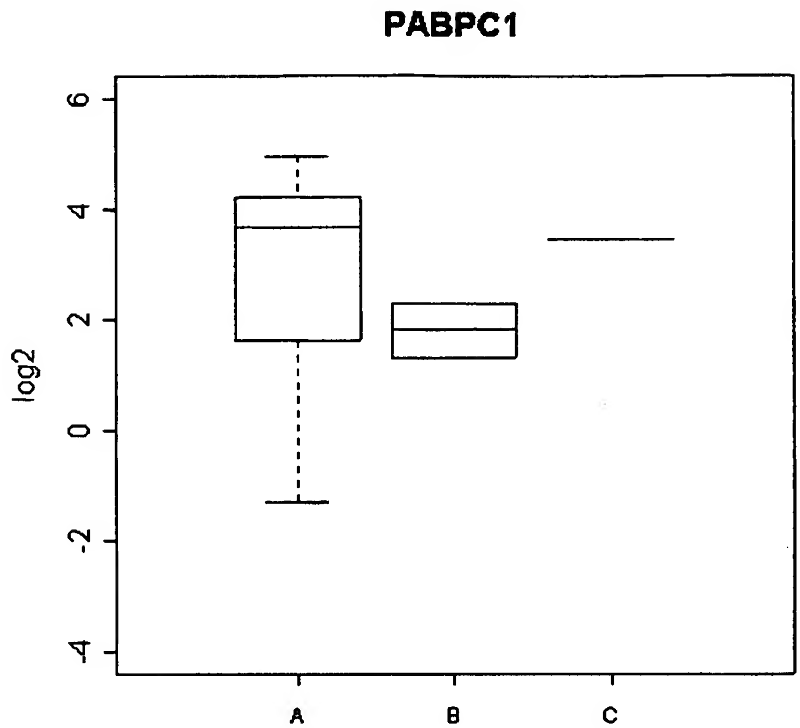
[Fig. 034]



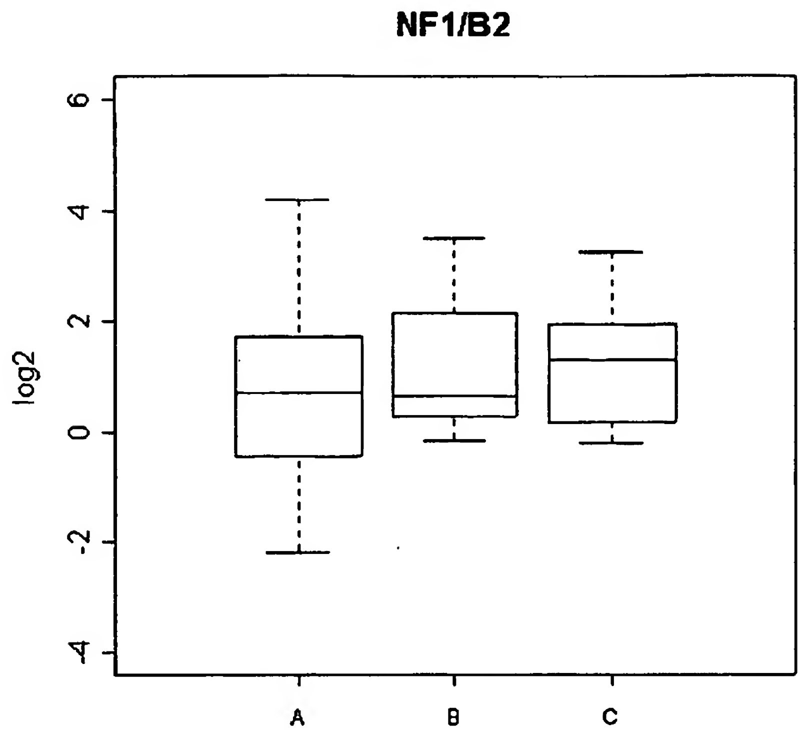
[Fig. 035]



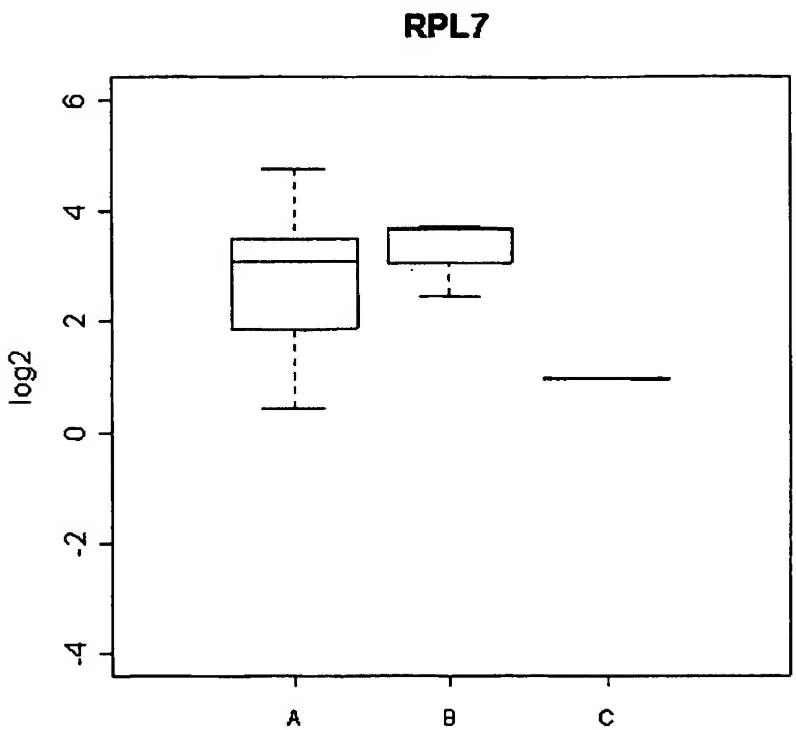
[Fig. 036]



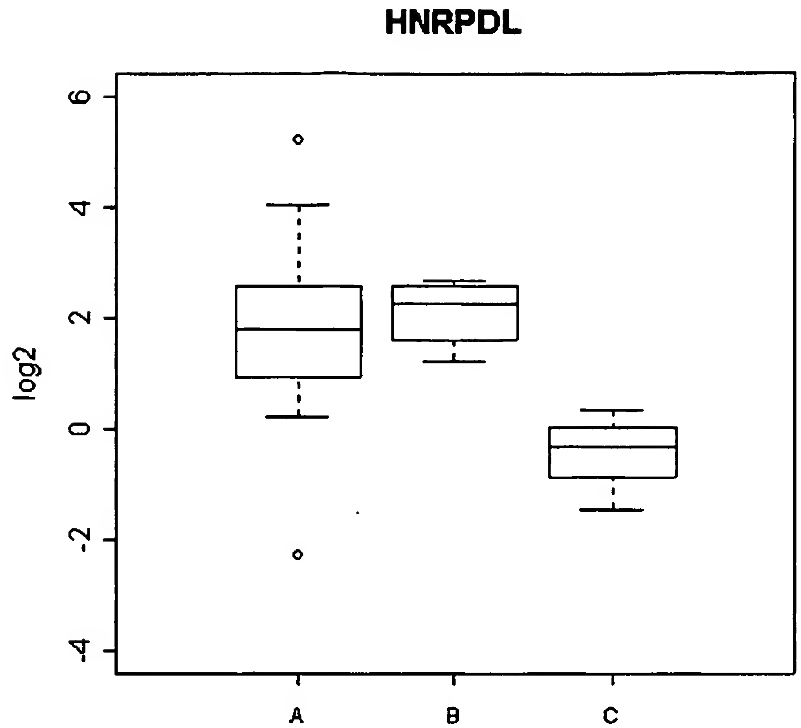
[Fig. 037]



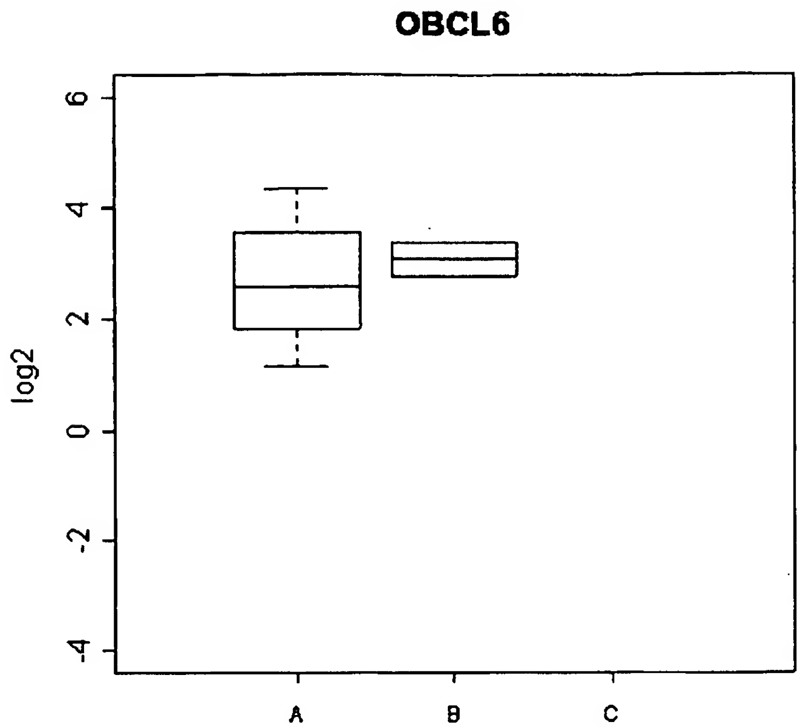
[Fig. 038]



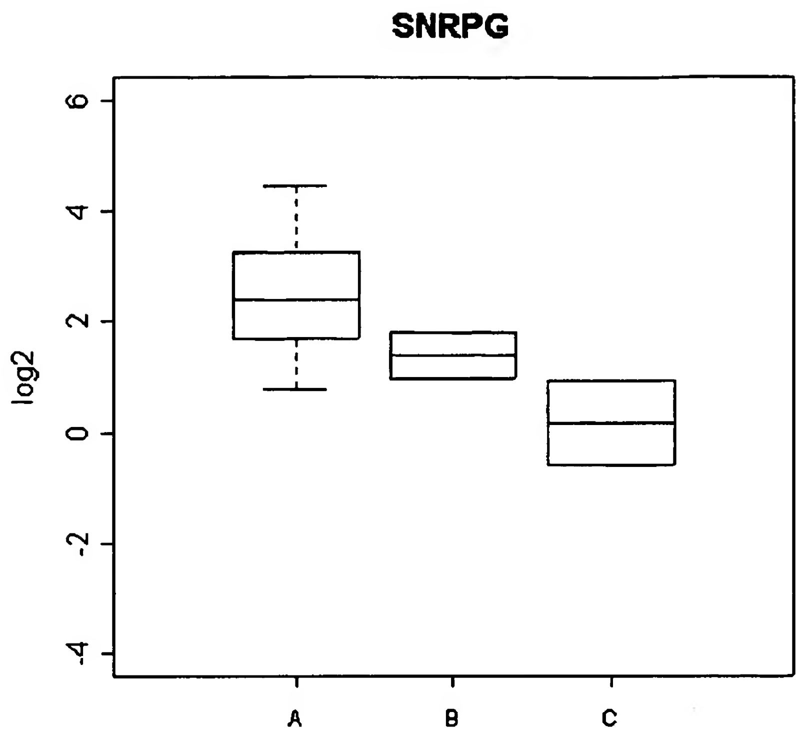
[Fig. 039]



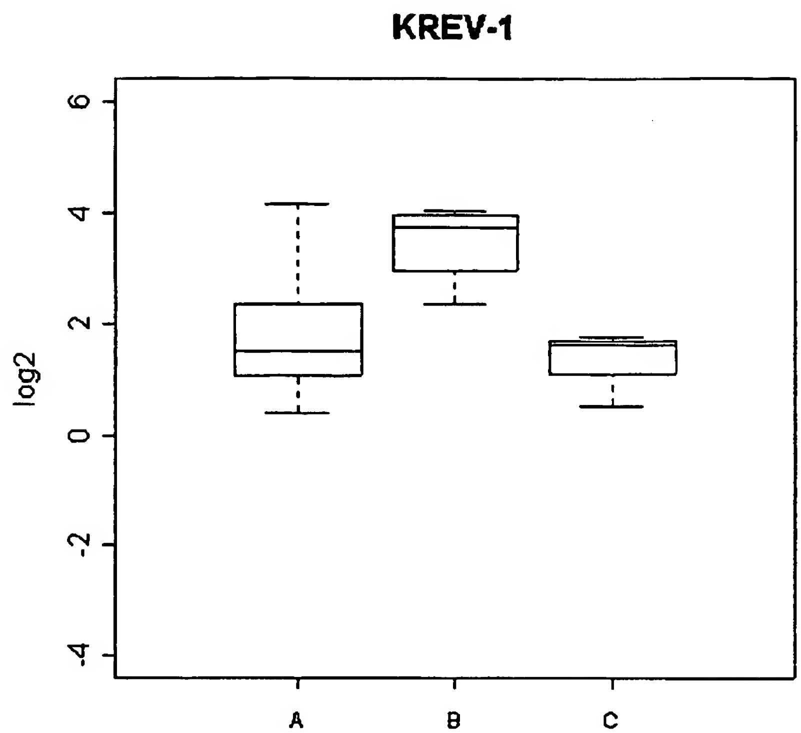
[Fig. 040]



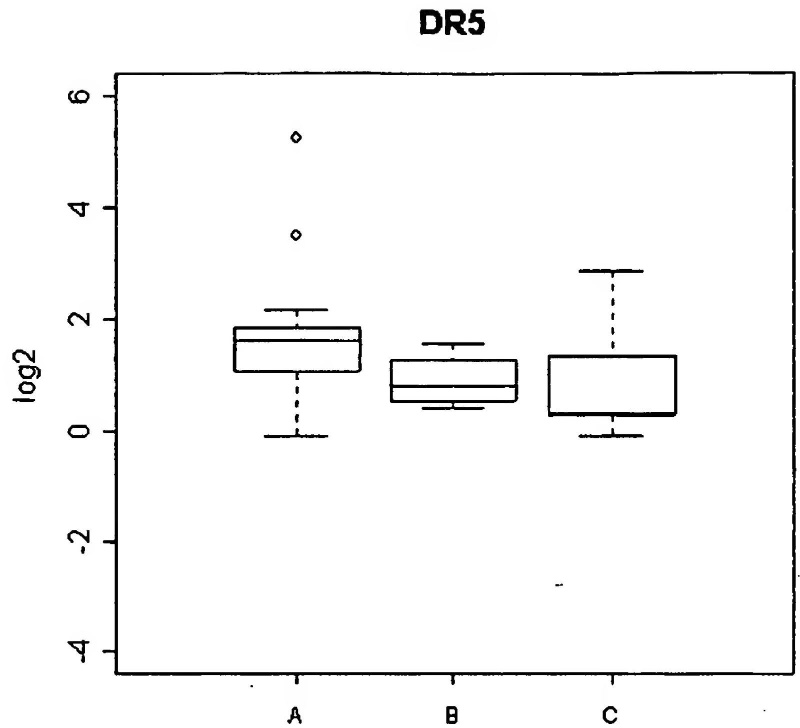
[Fig. 041]



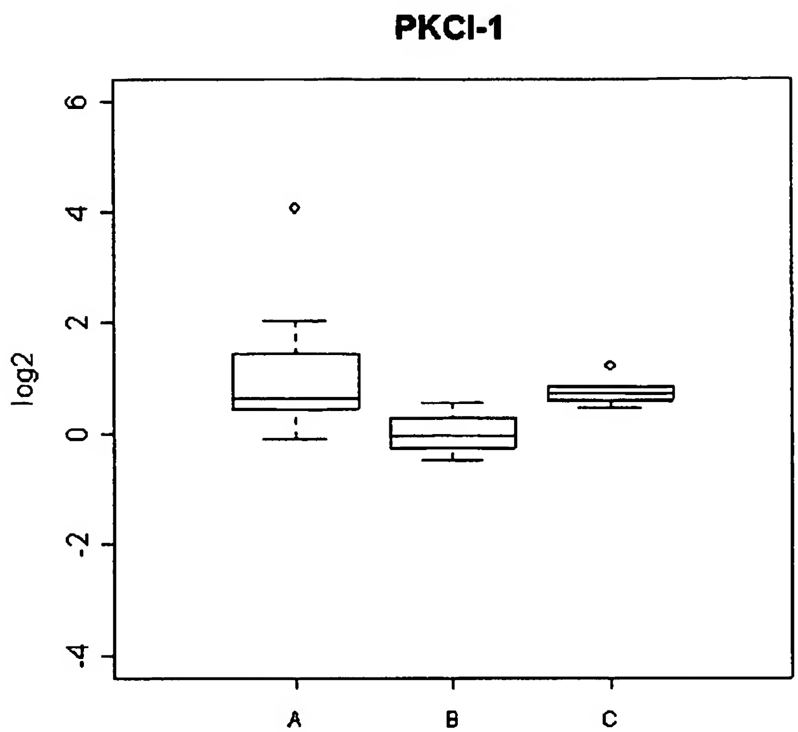
[Fig. 042]



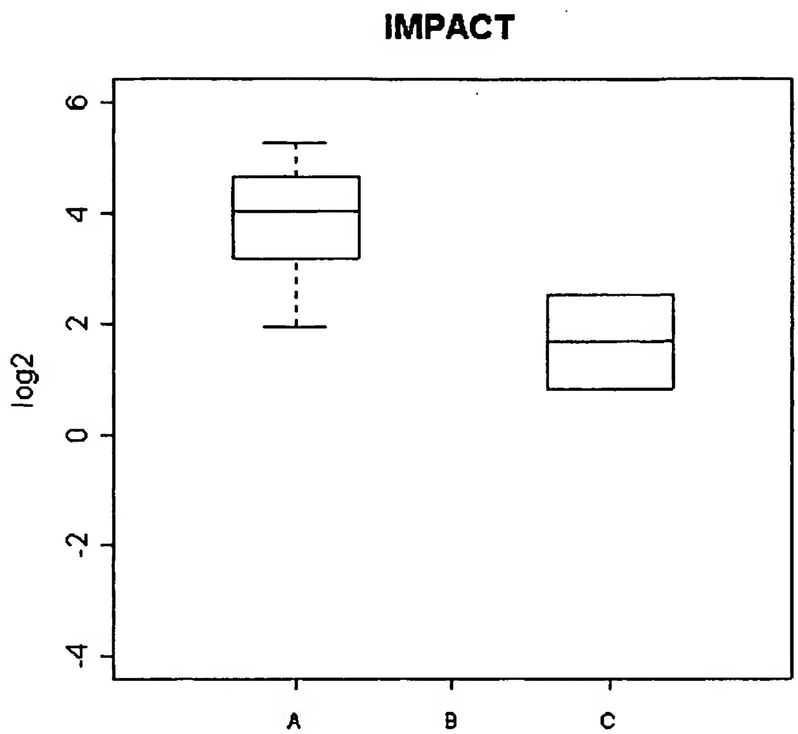
[Fig. 043]



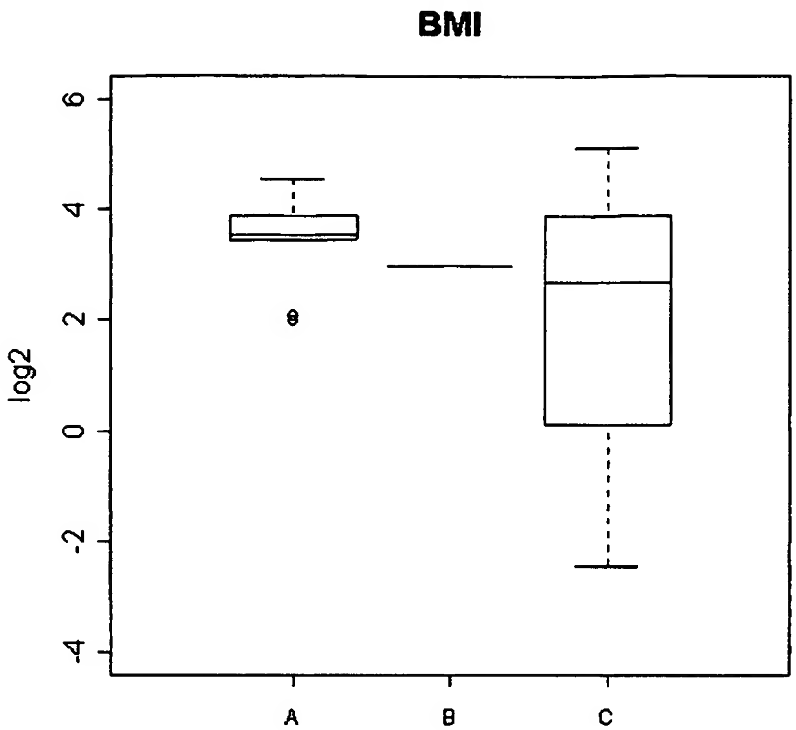
[Fig. 044]



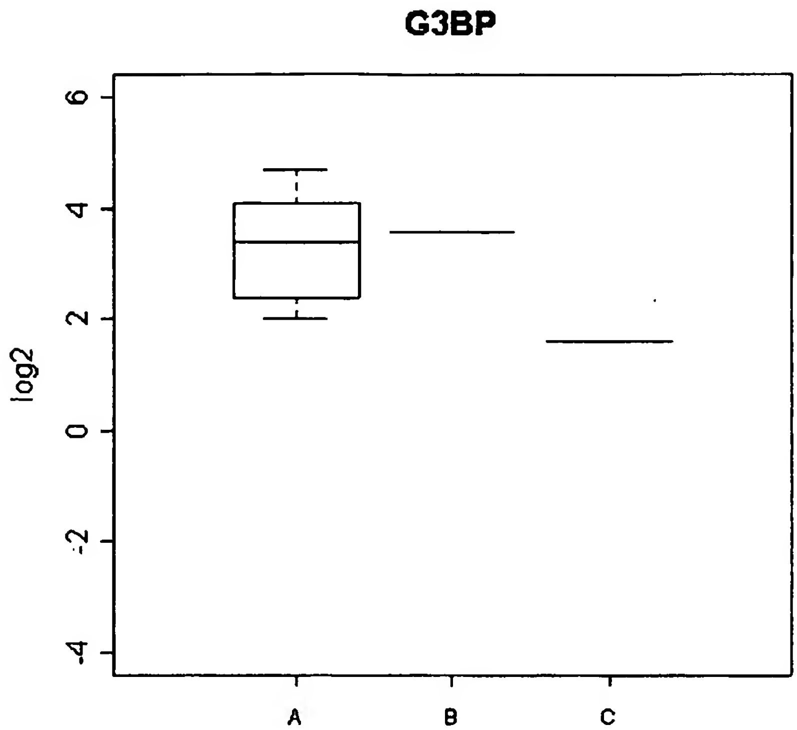
[Fig. 045]



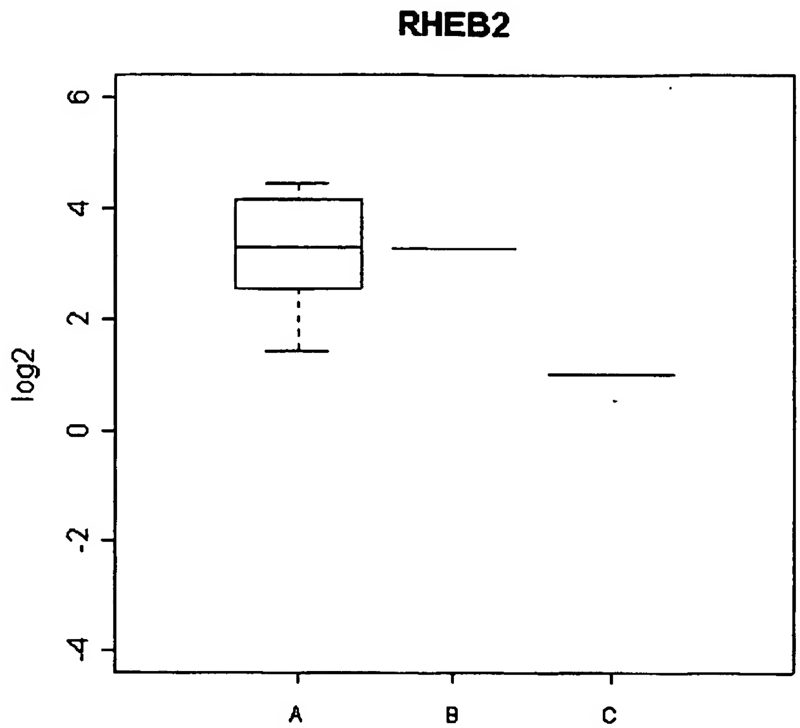
[Fig. 046]



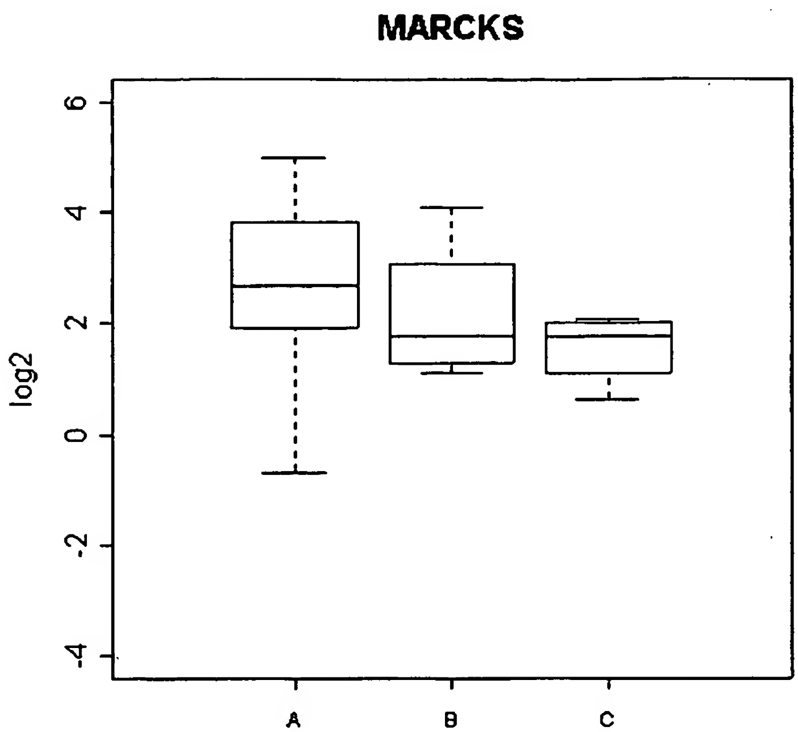
[Fig. 047]



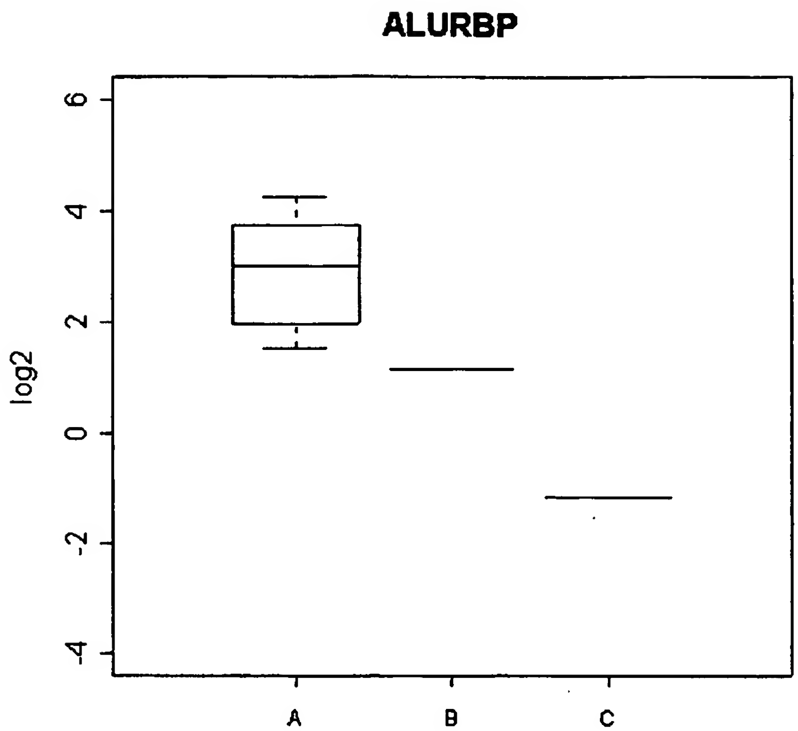
[Fig. 048]



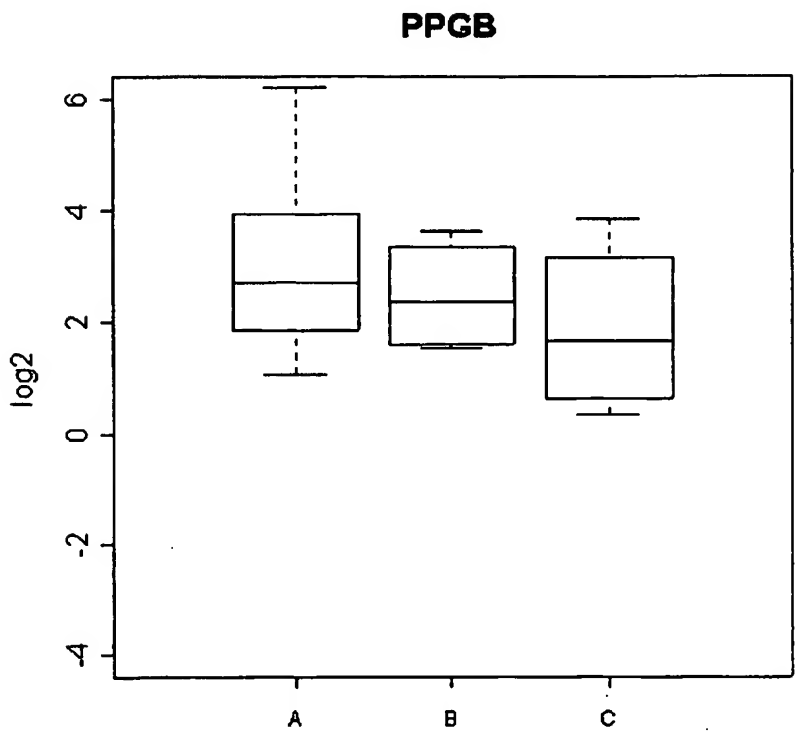
[Fig. 049]



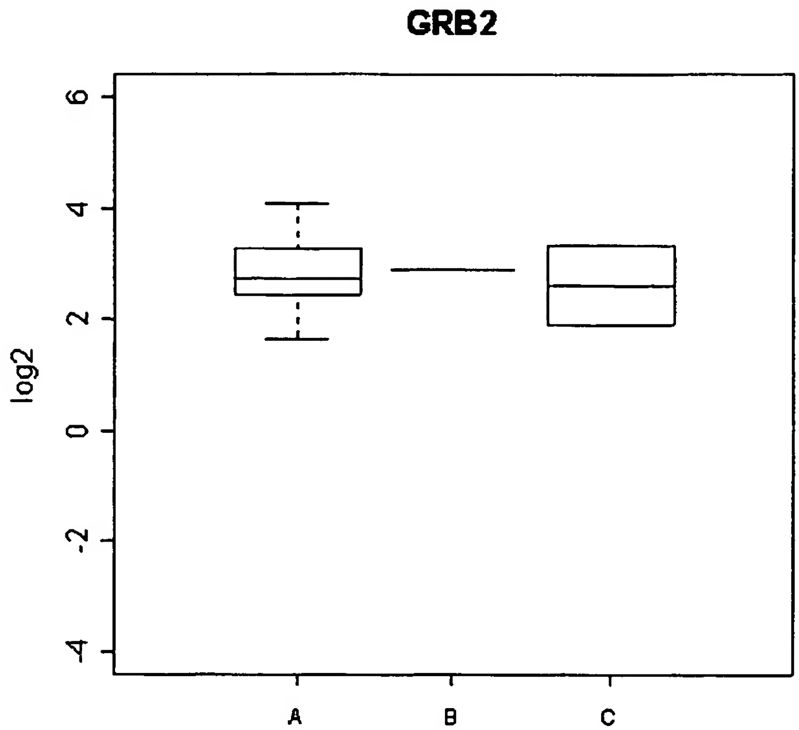
[Fig. 050]



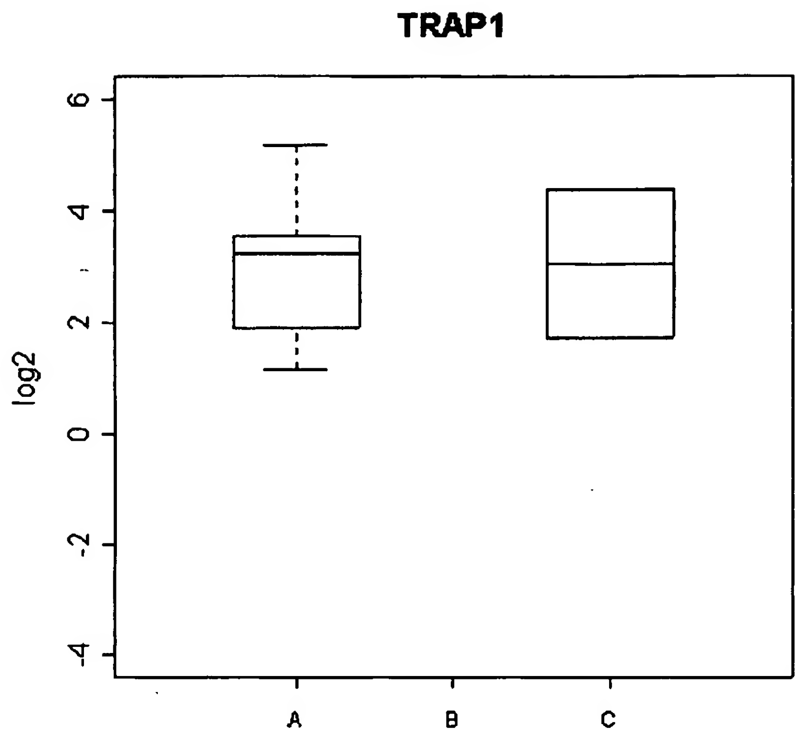
[Fig. 051]



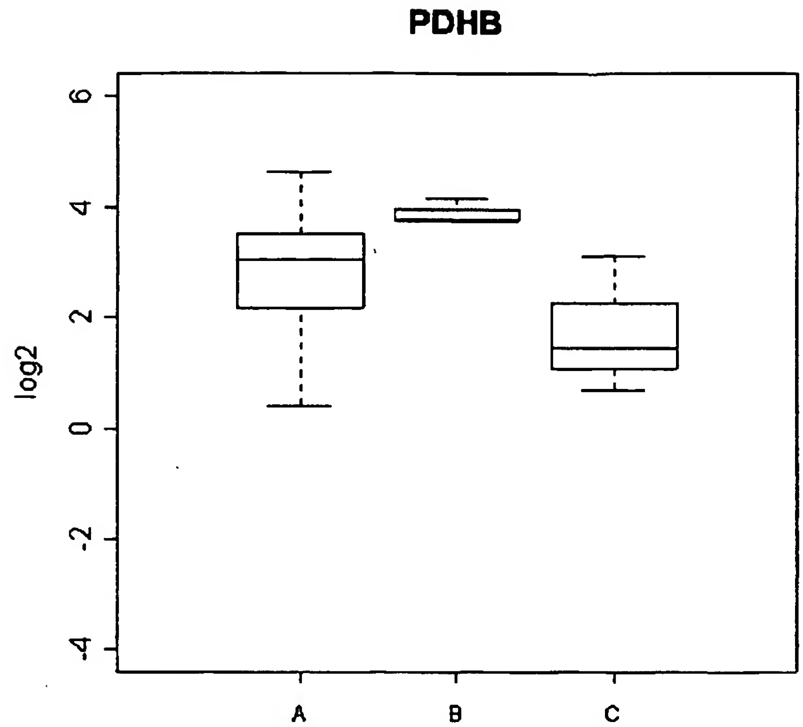
[Fig. 052]



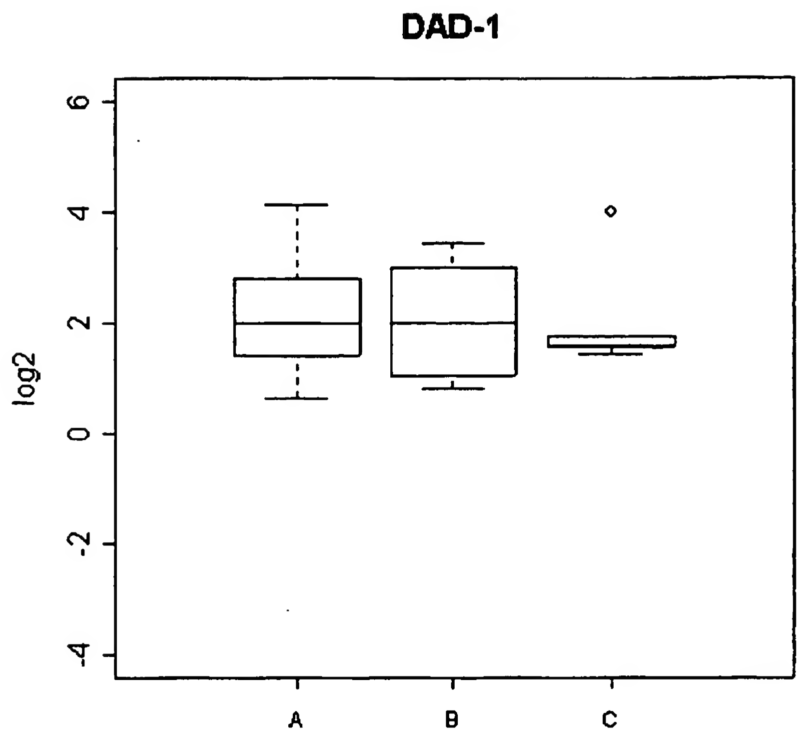
[Fig. 053]



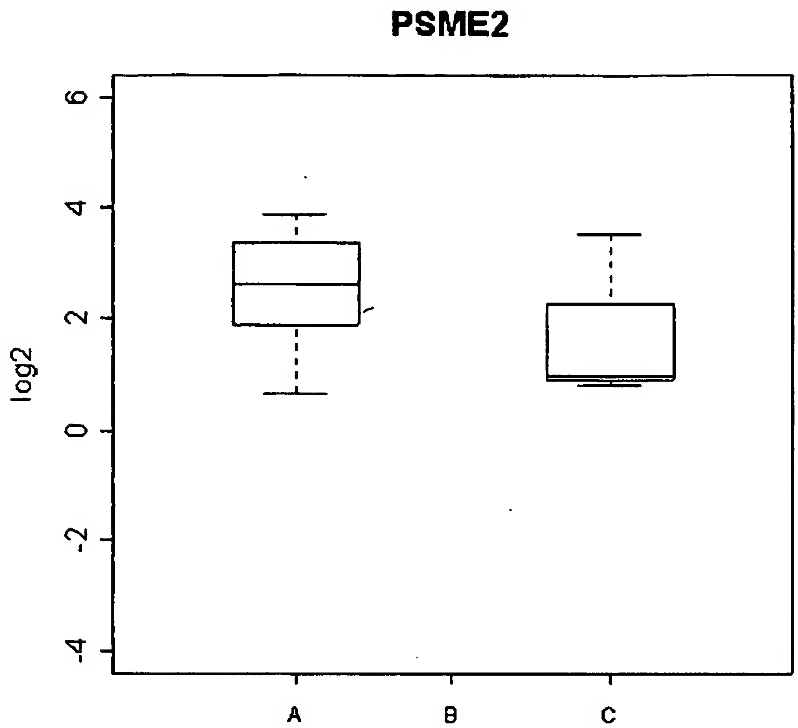
[Fig. 054]



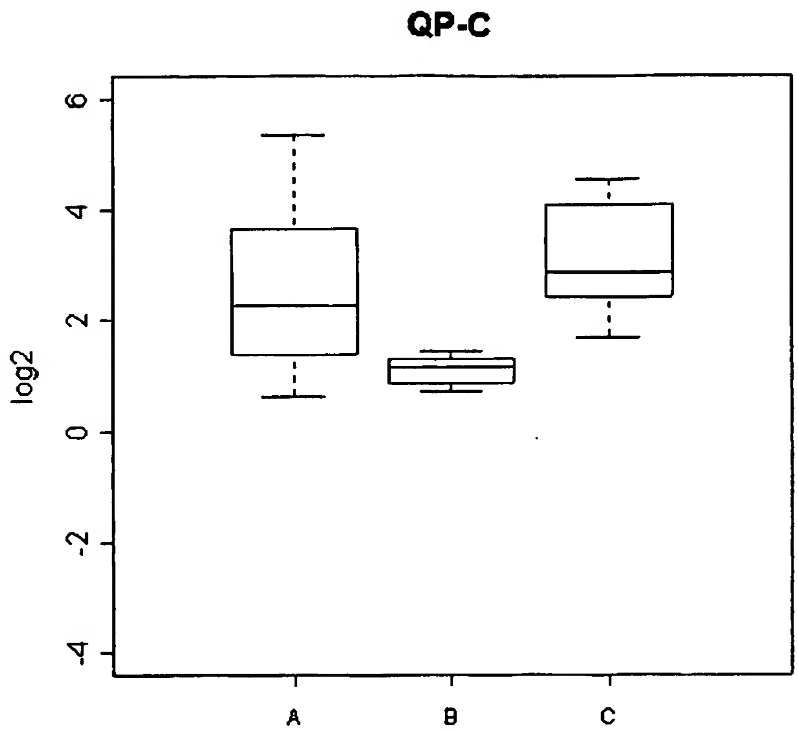
[Fig. 055]



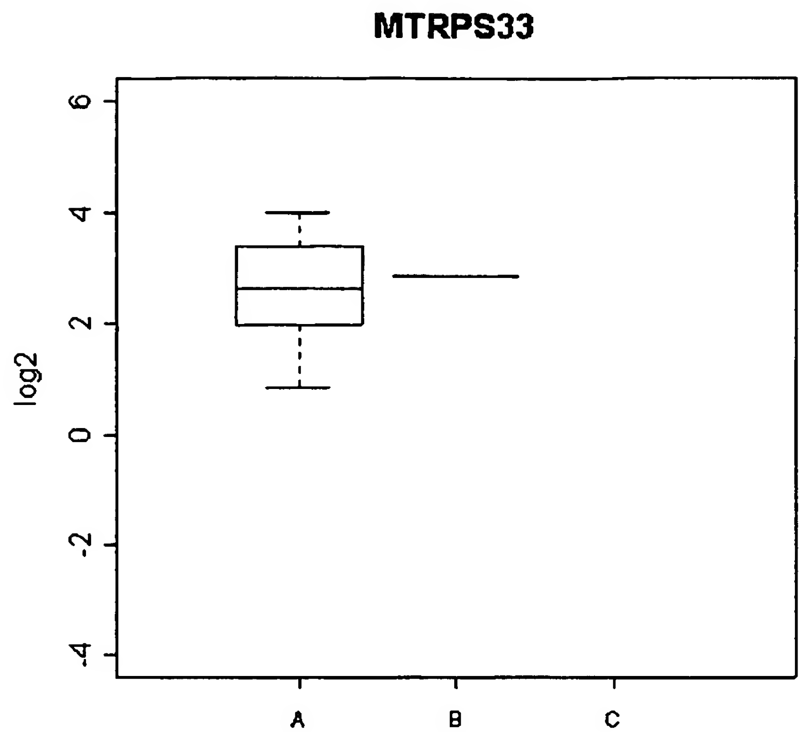
[Fig. 056]



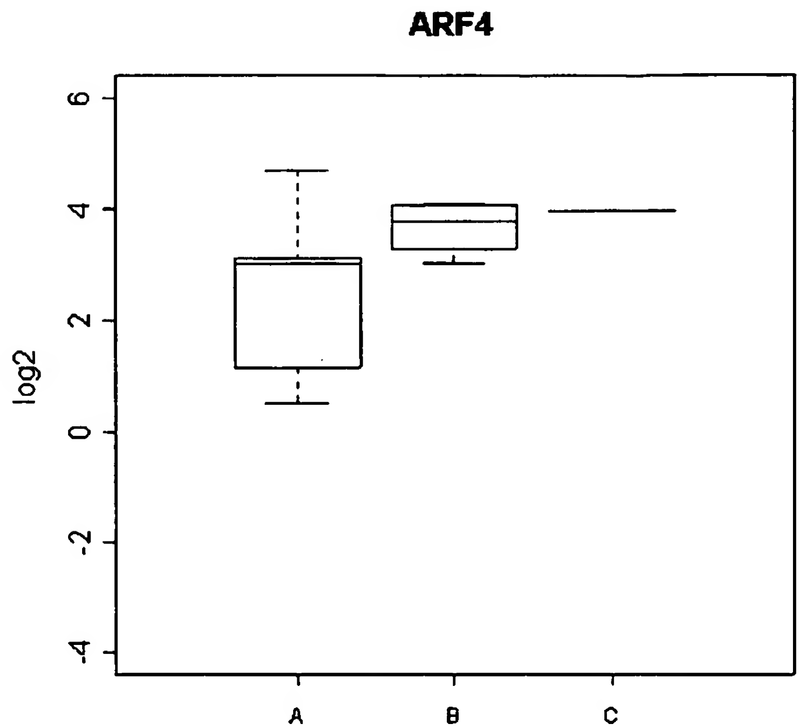
[Fig. 057]



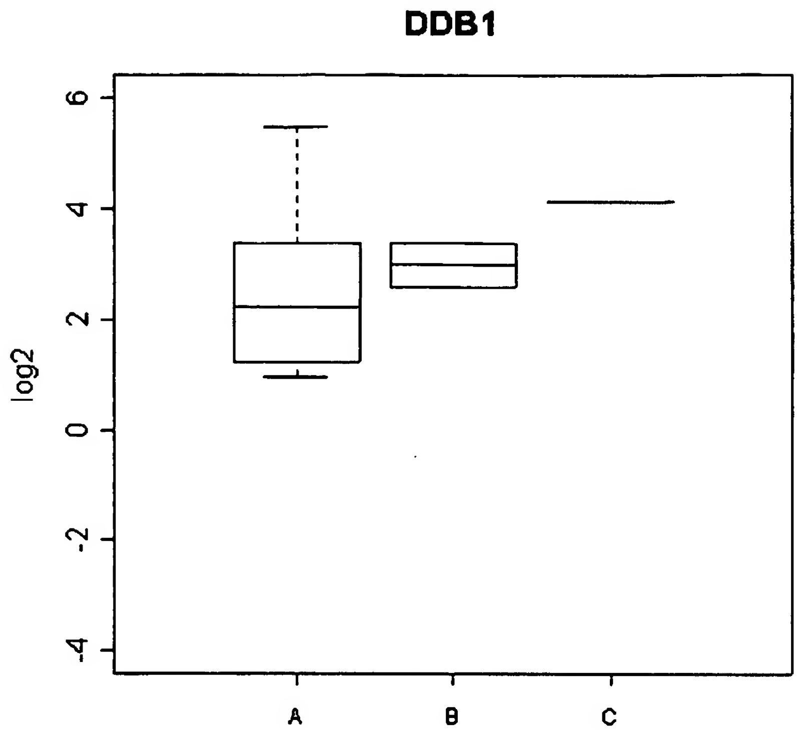
[Fig. 058]



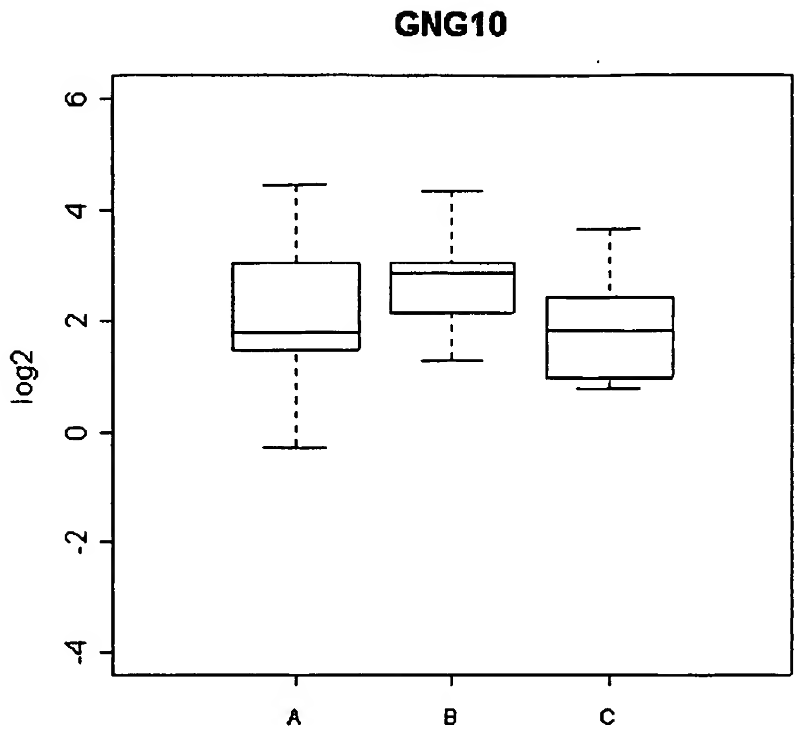
[Fig. 059]



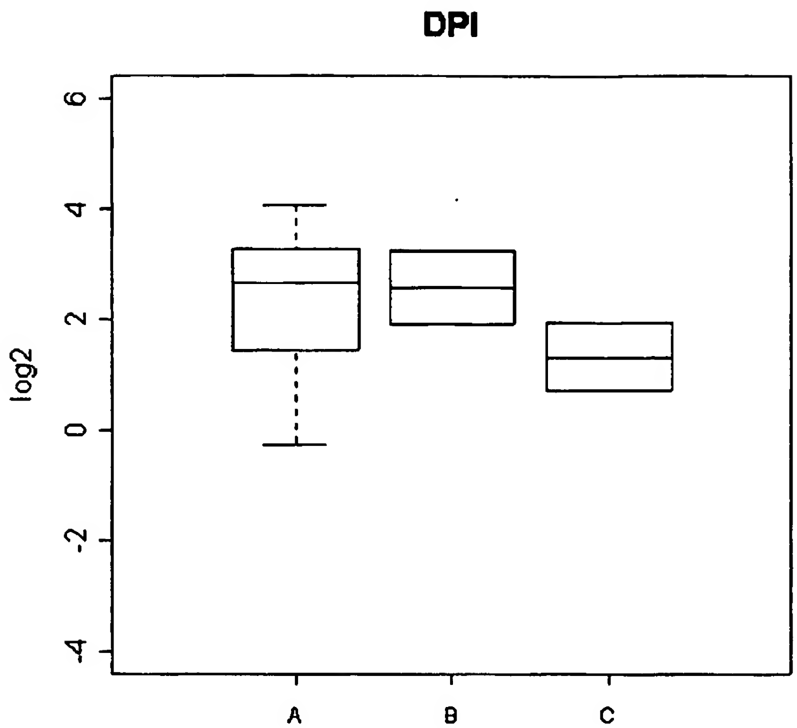
[Fig. 060]



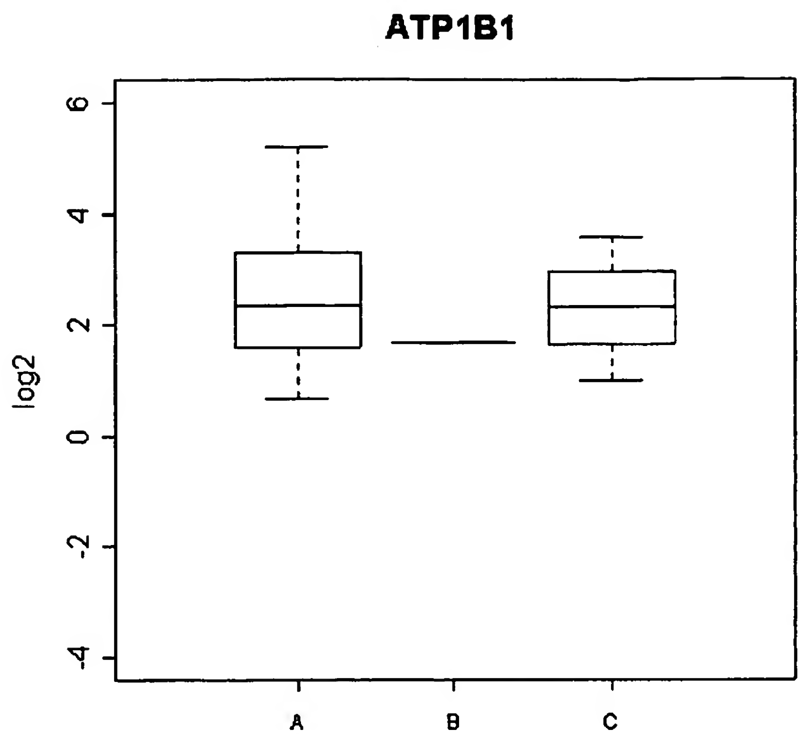
[Fig. 061]



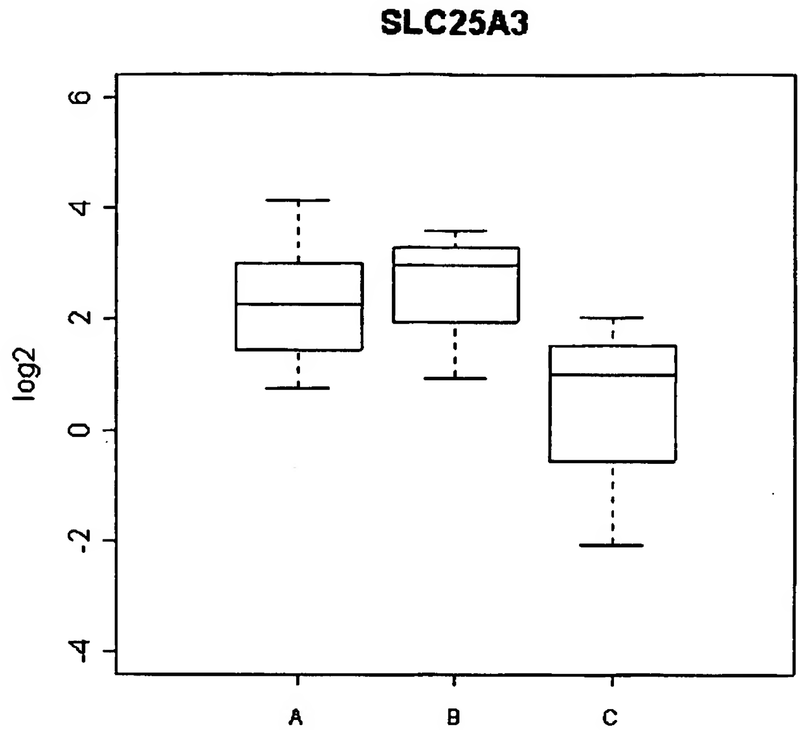
[Fig. 062]



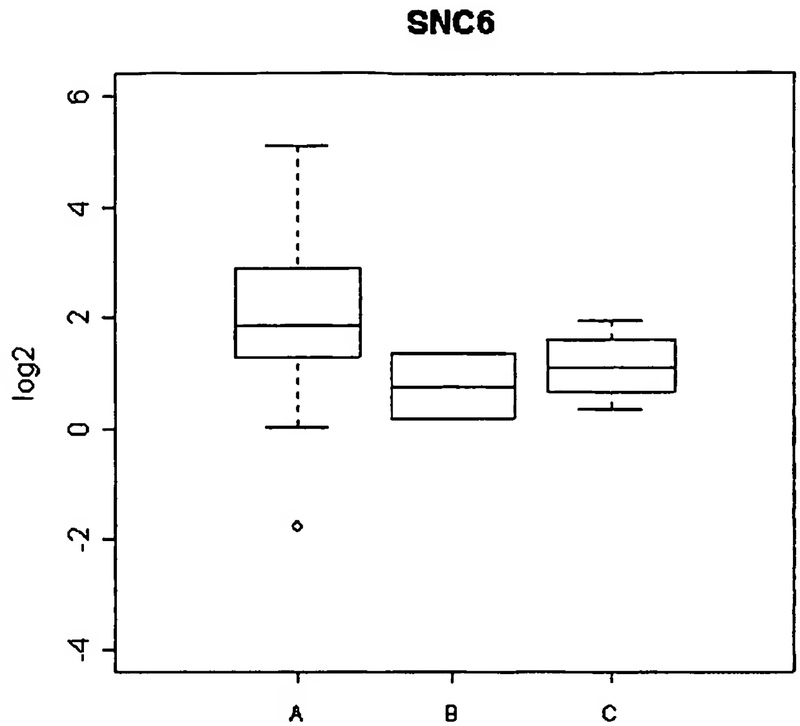
[Fig. 063]



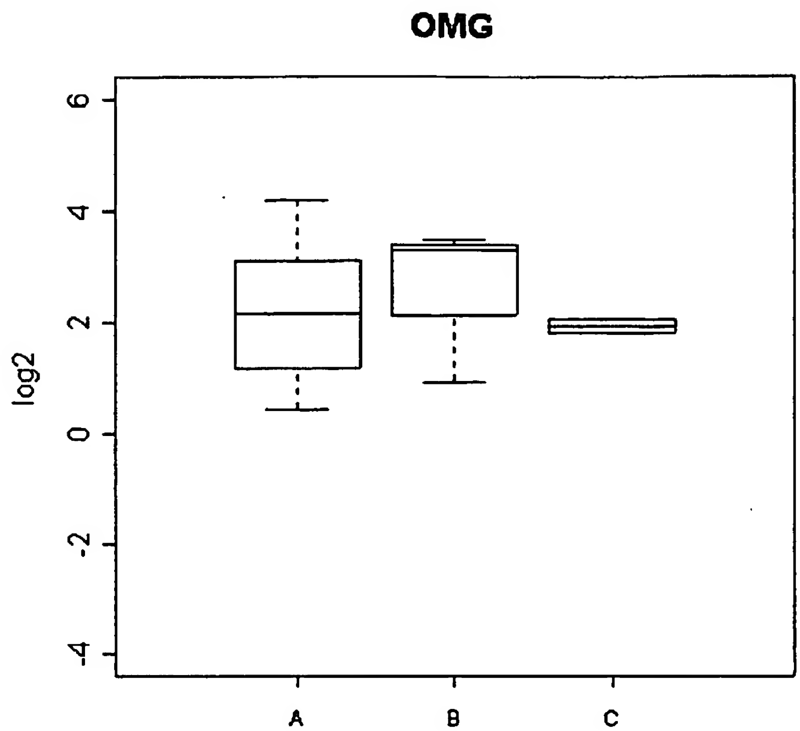
[Fig. 064]



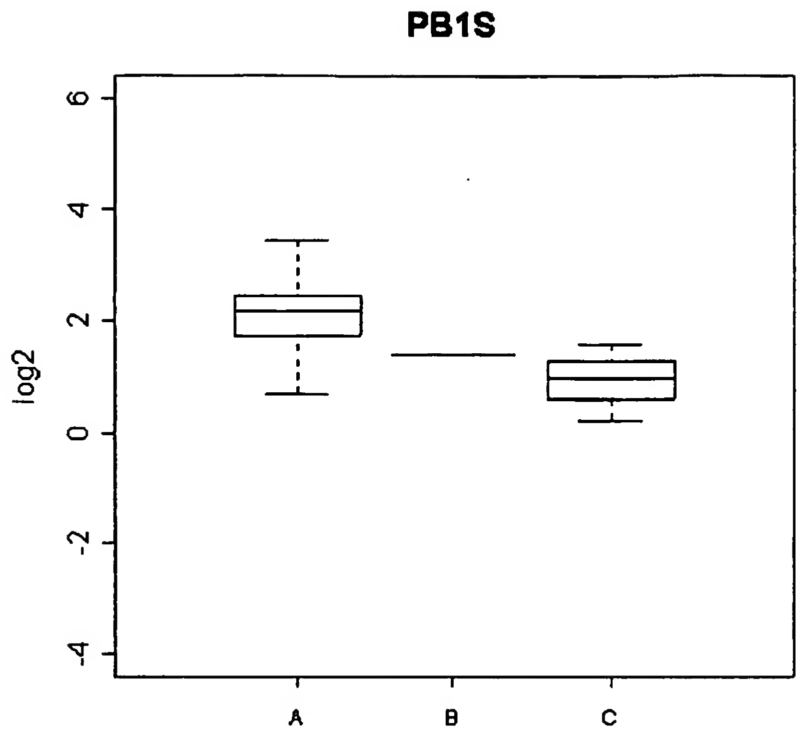
[Fig. 065]



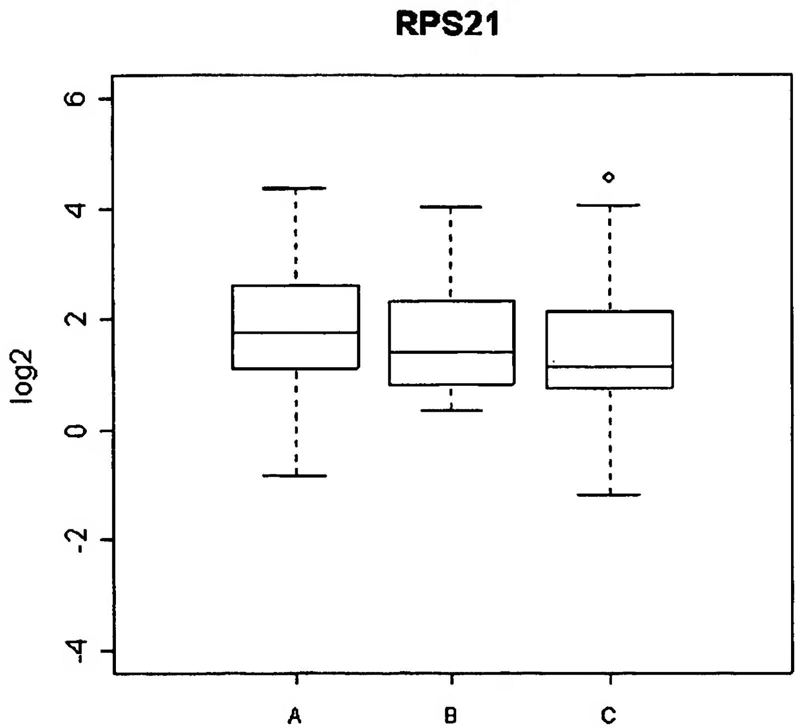
[Fig. 066]



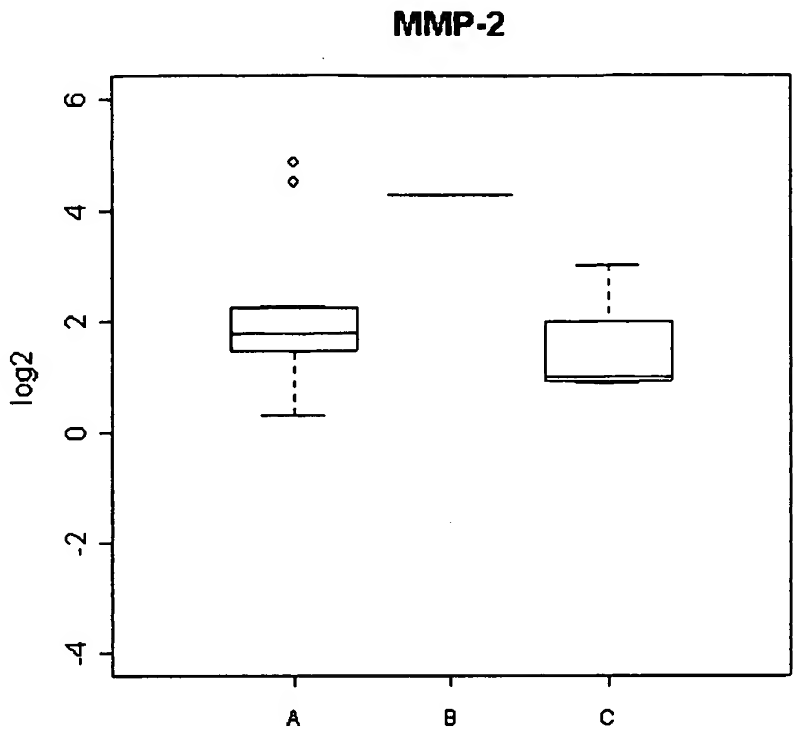
[Fig. 067]



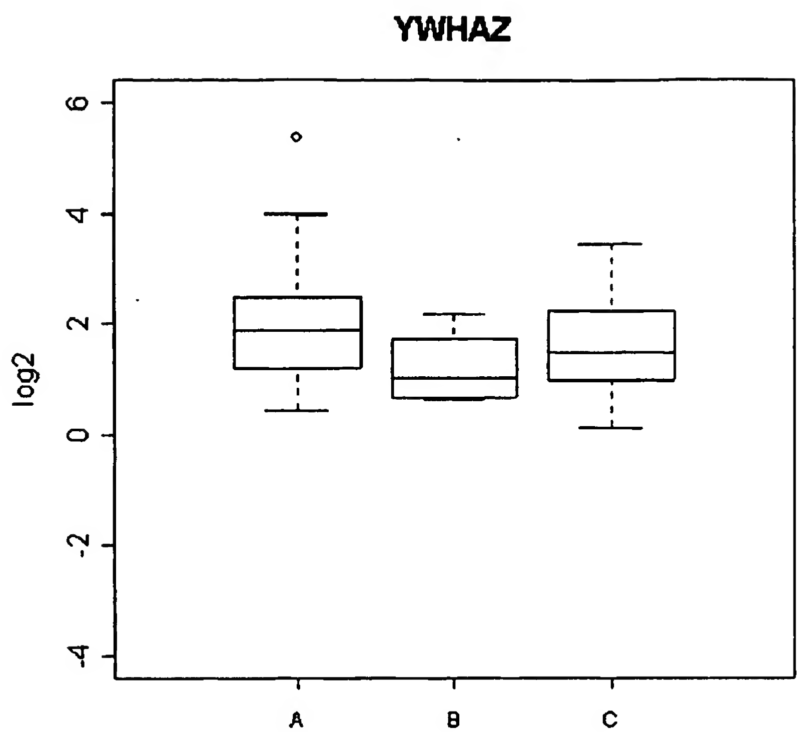
[Fig. 068]



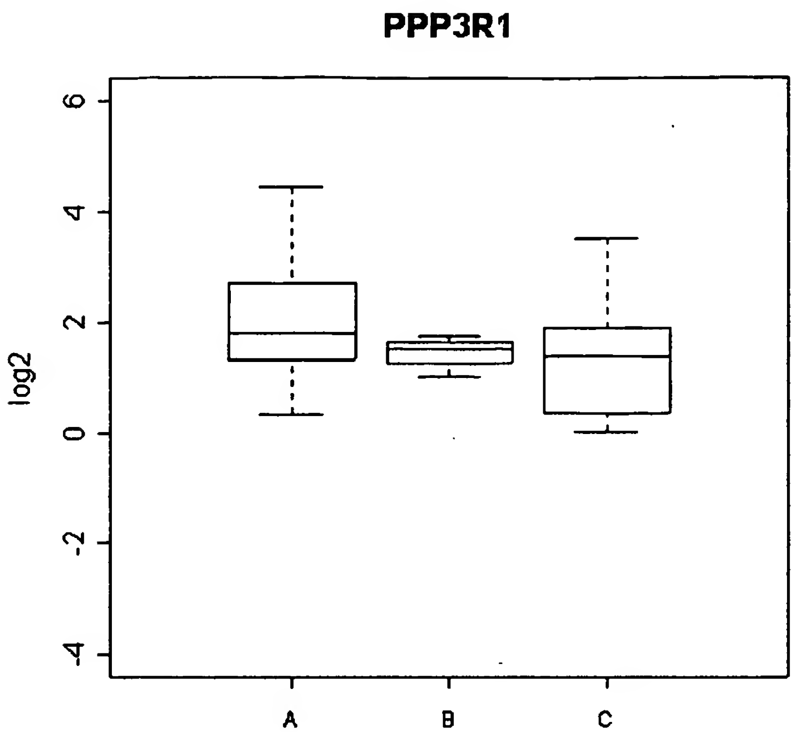
[Fig. 069]



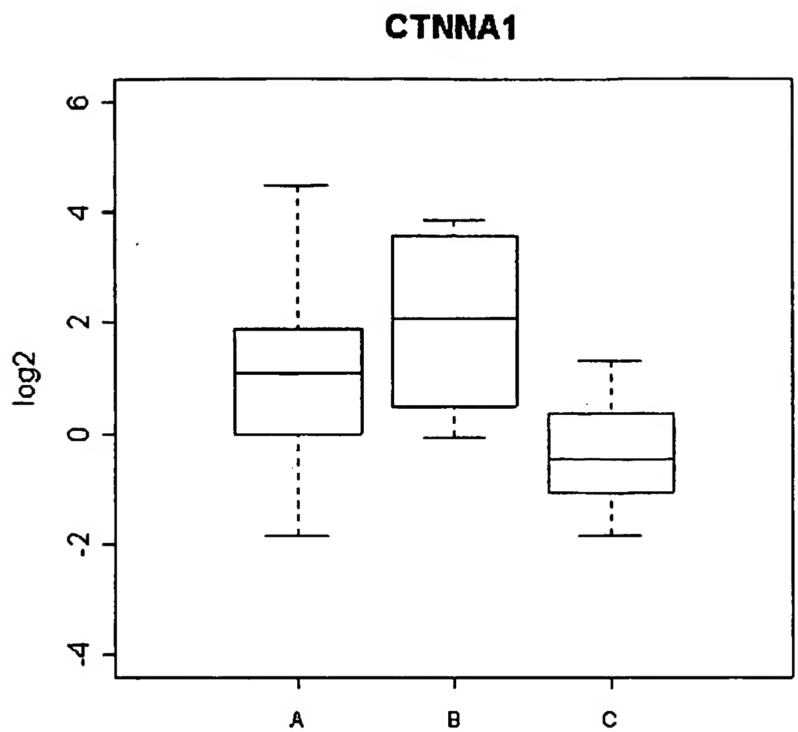
[Fig. 070]



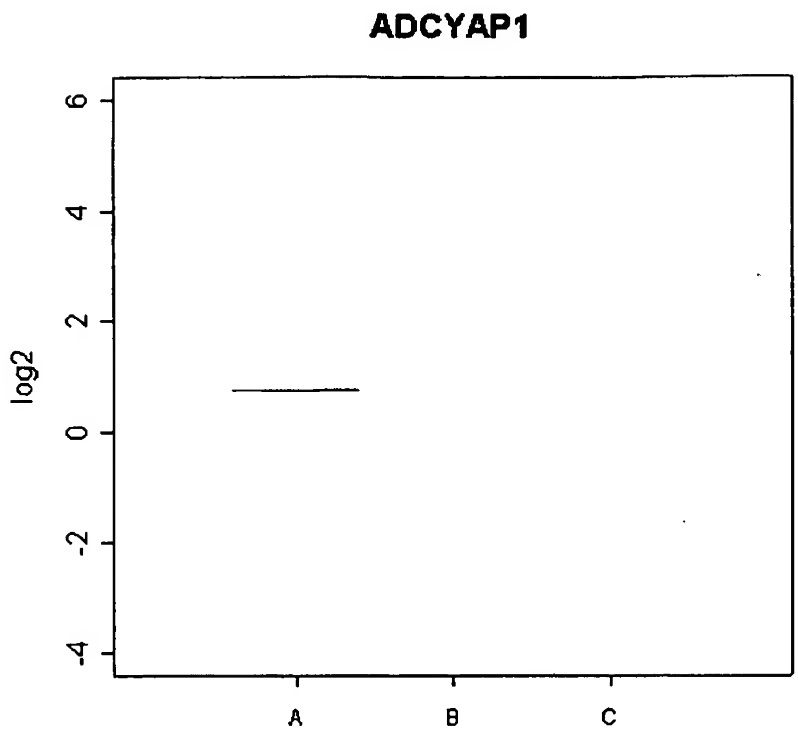
[Fig. 071]



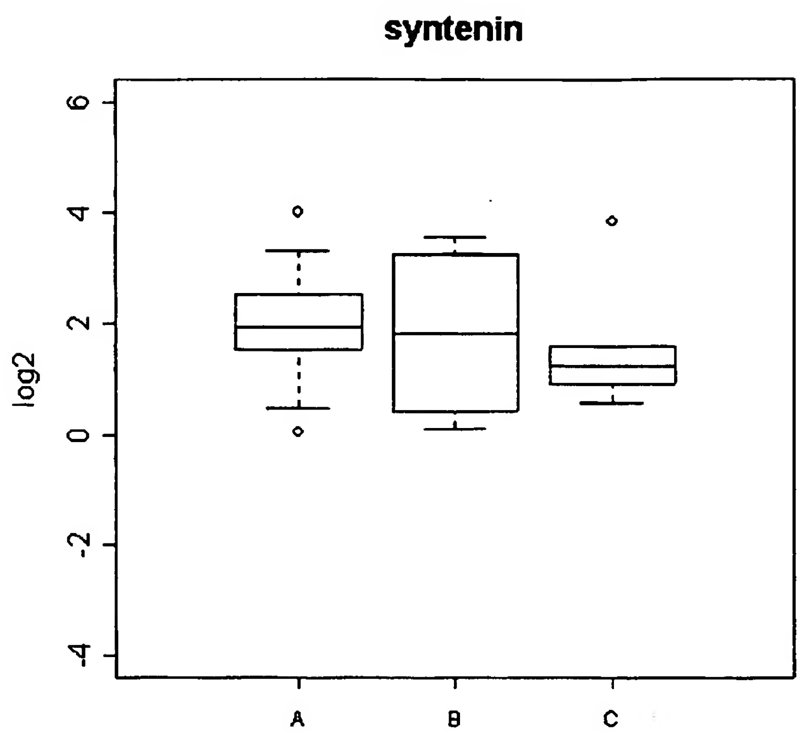
[Fig. 072]



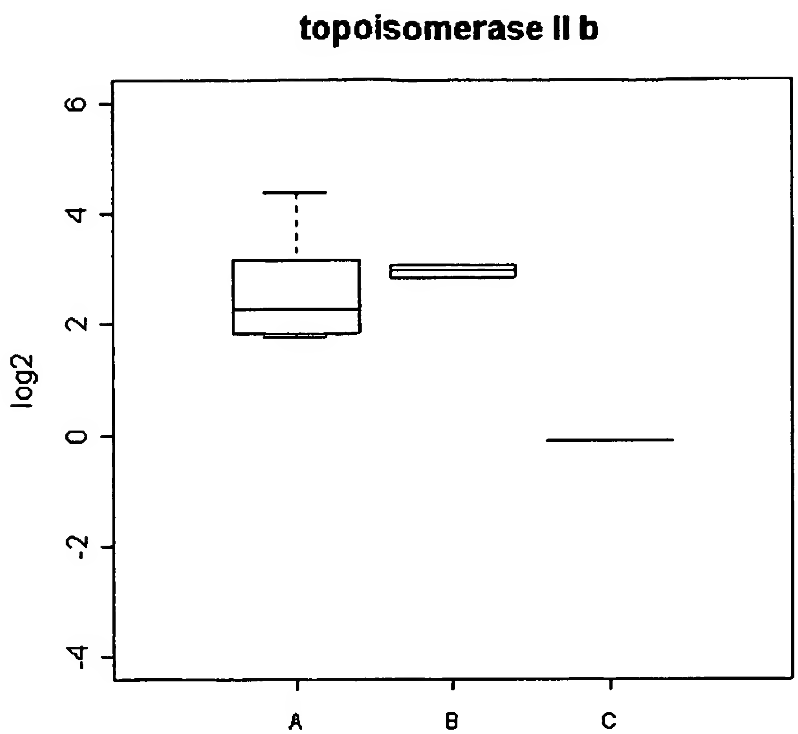
[Fig. 073]



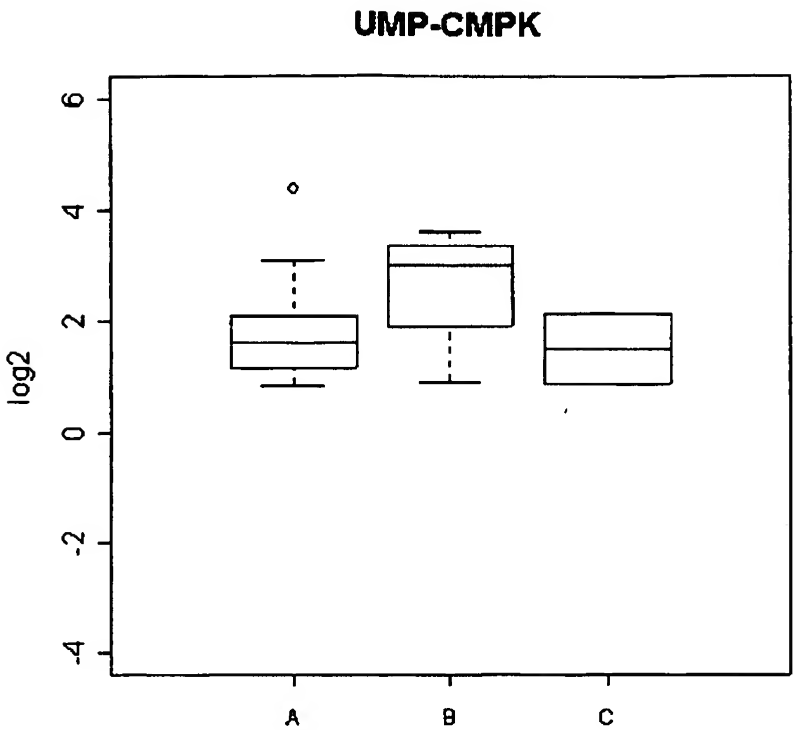
[Fig. 074]



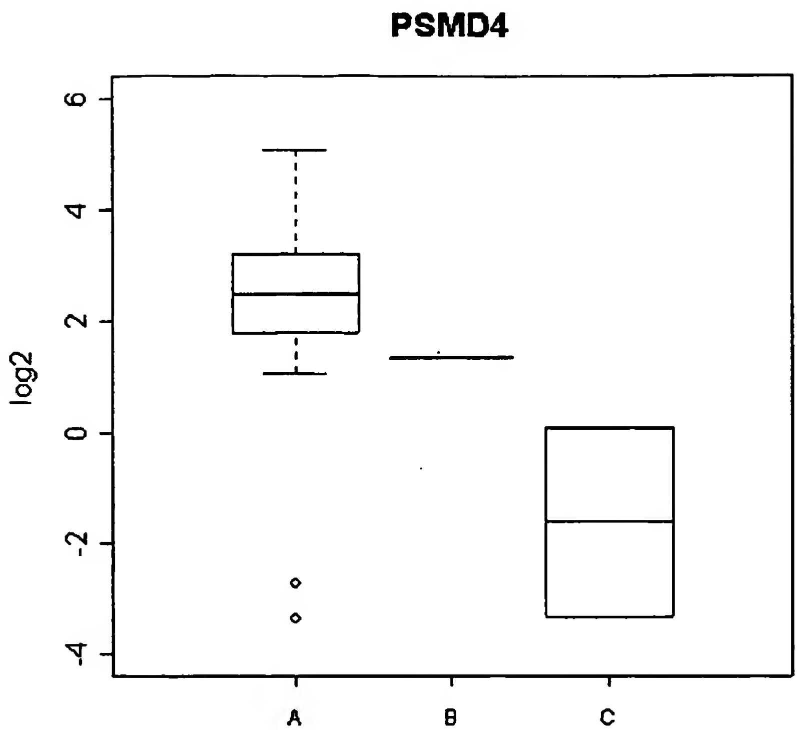
[Fig. 075]



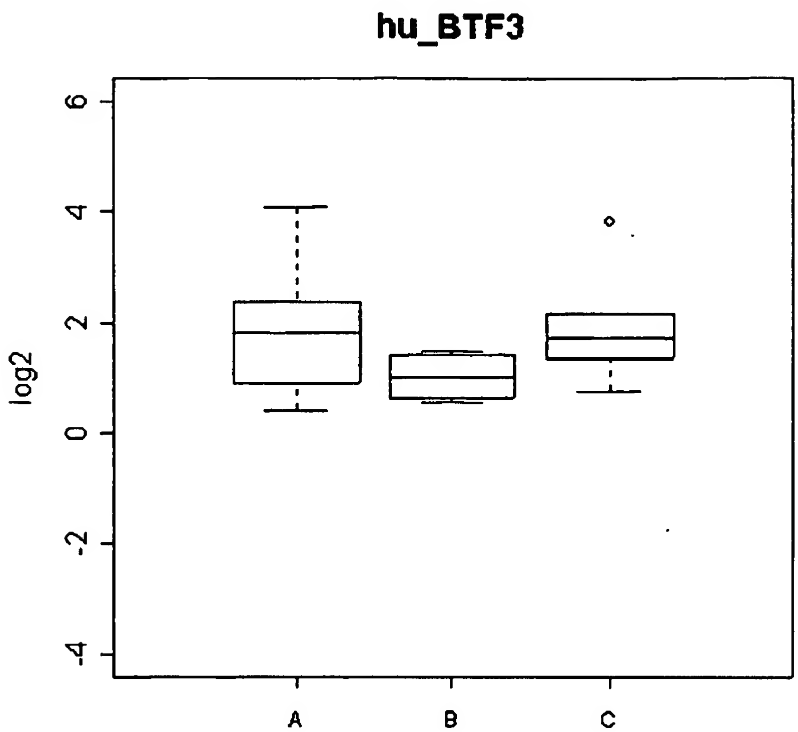
[Fig. 076]



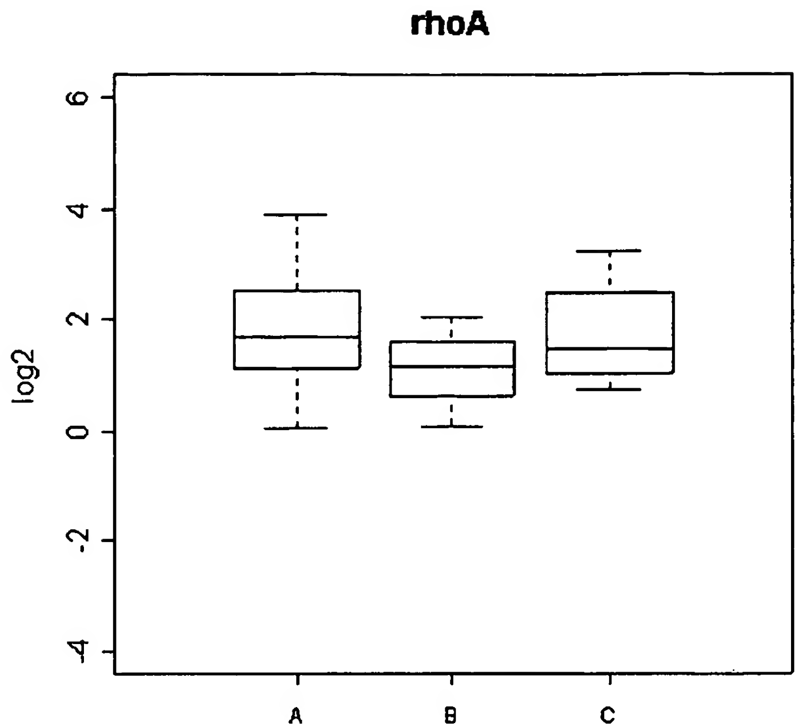
[Fig. 077]



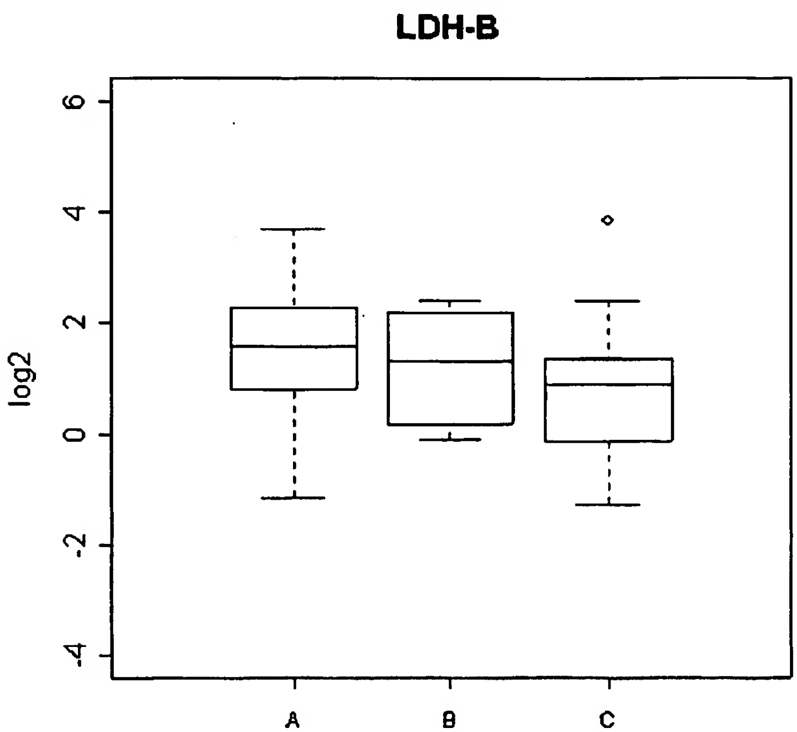
[Fig. 078]



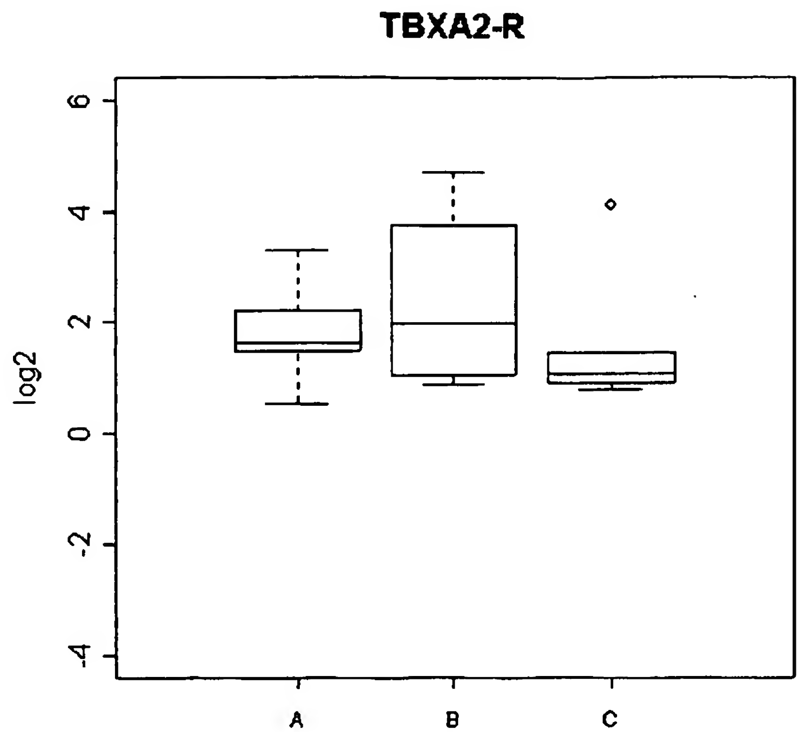
[Fig. 079]



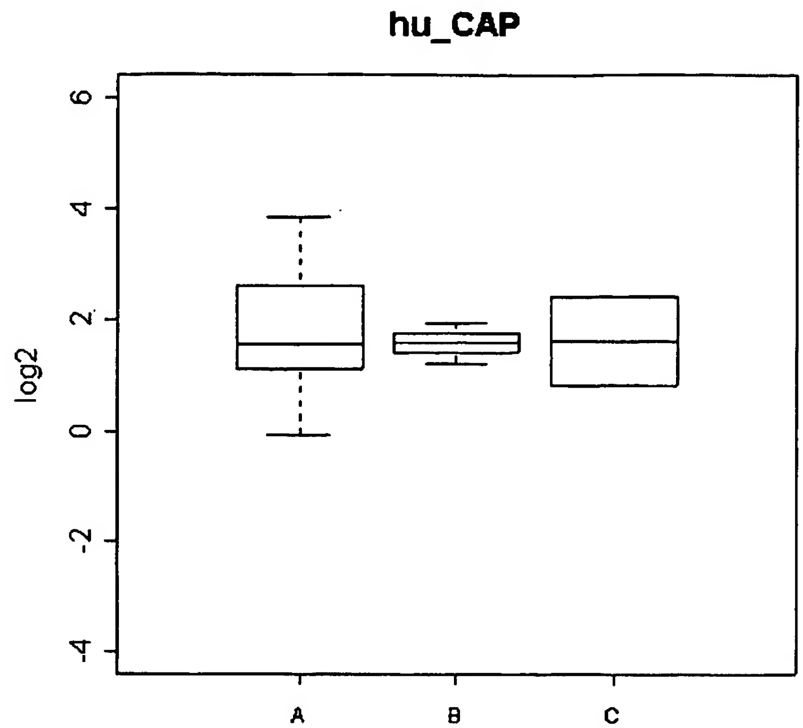
[Fig. 080]



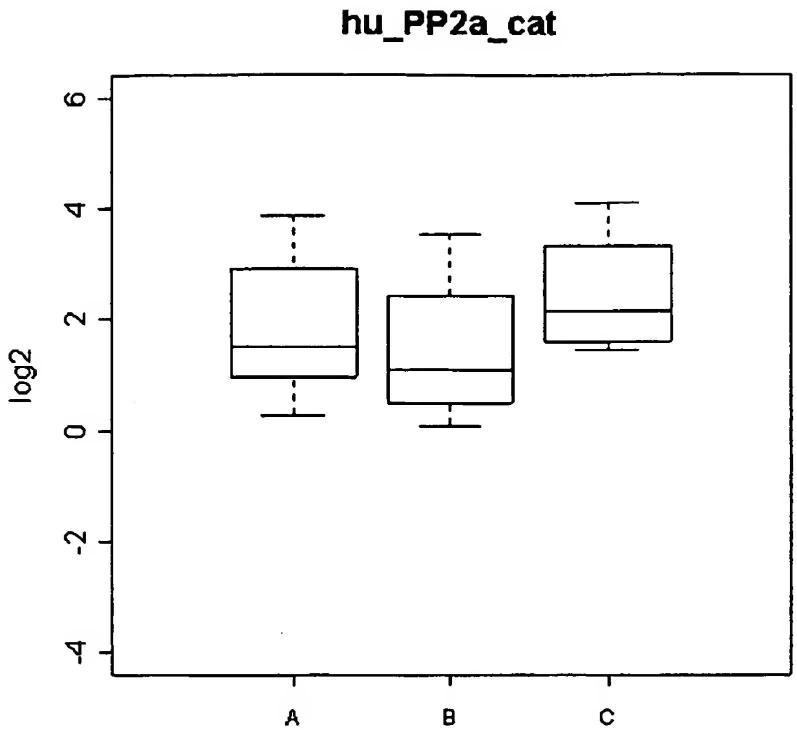
[Fig. 081]



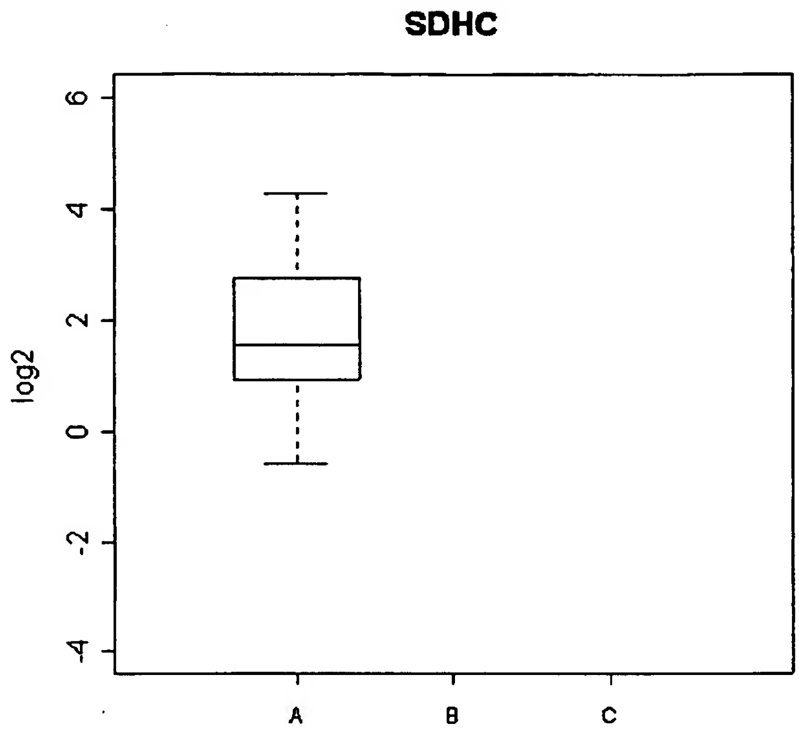
[Fig. 082]



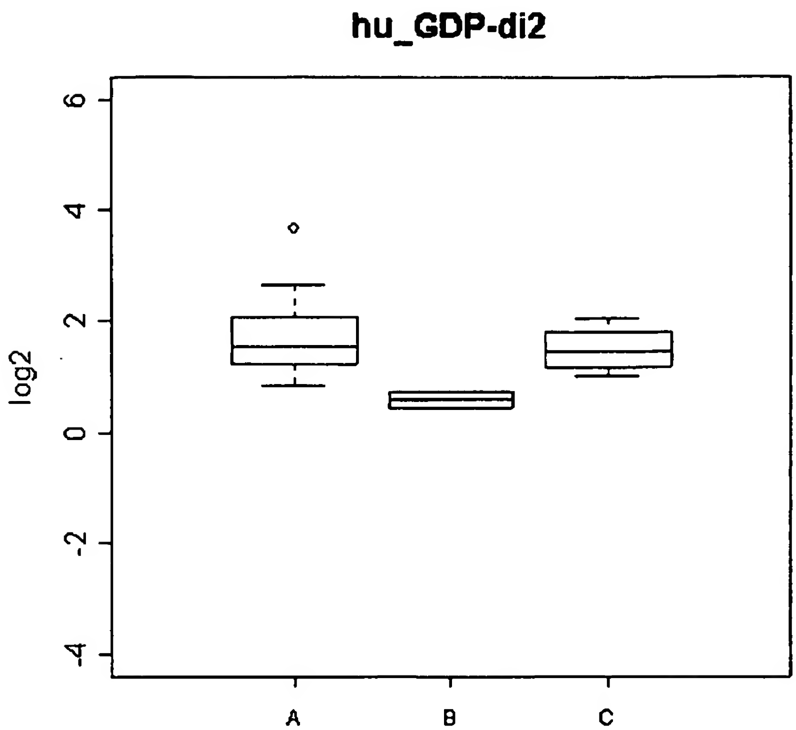
[Fig. 083]



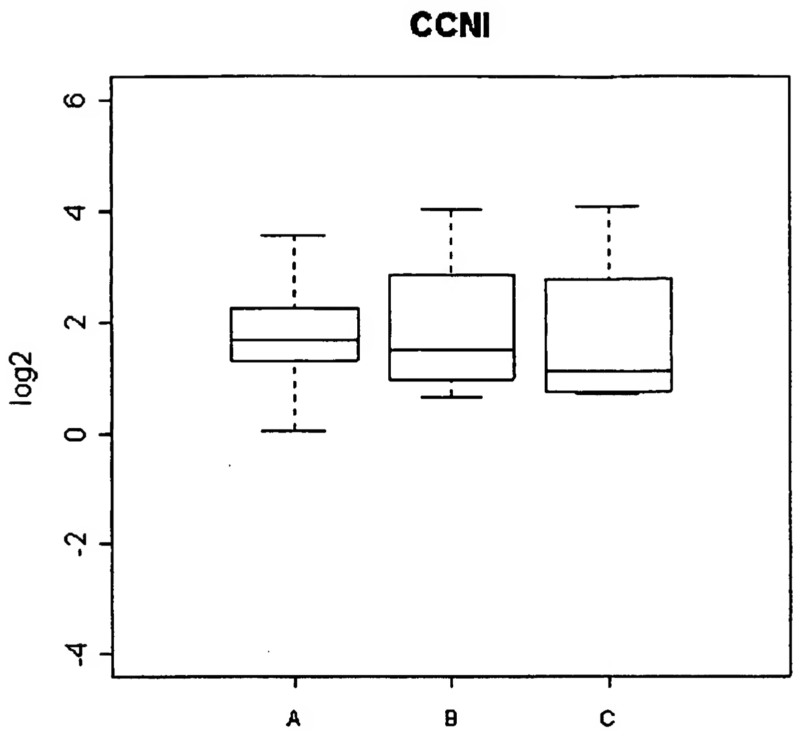
[Fig. 084]



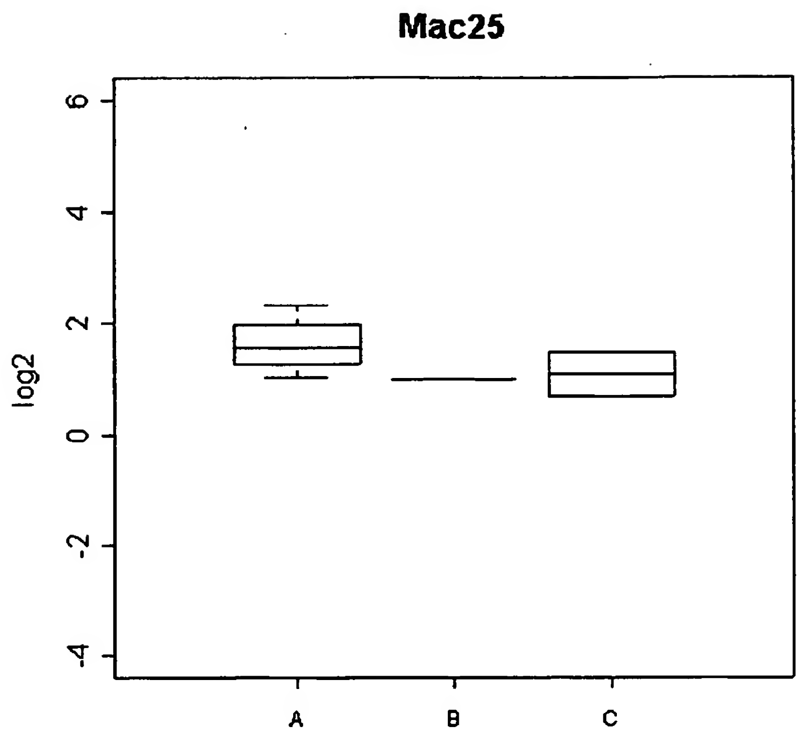
[Fig. 085]



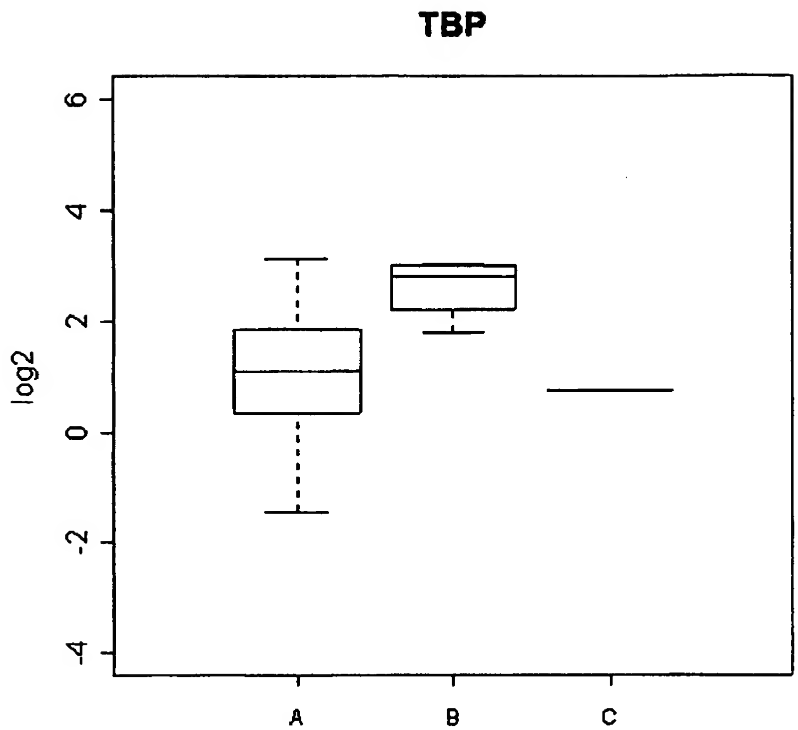
[Fig. 086]



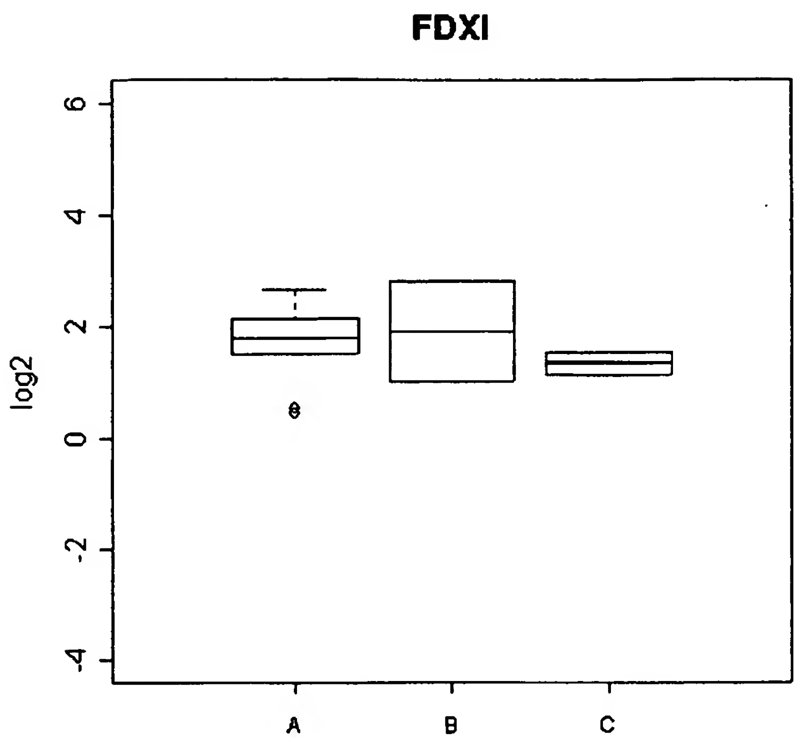
[Fig. 087]



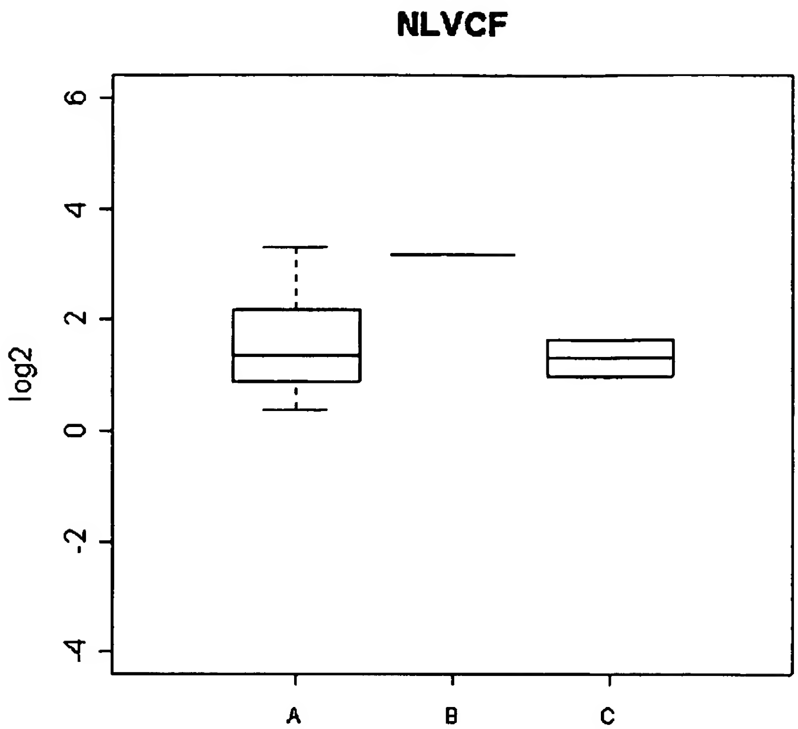
[Fig. 088]



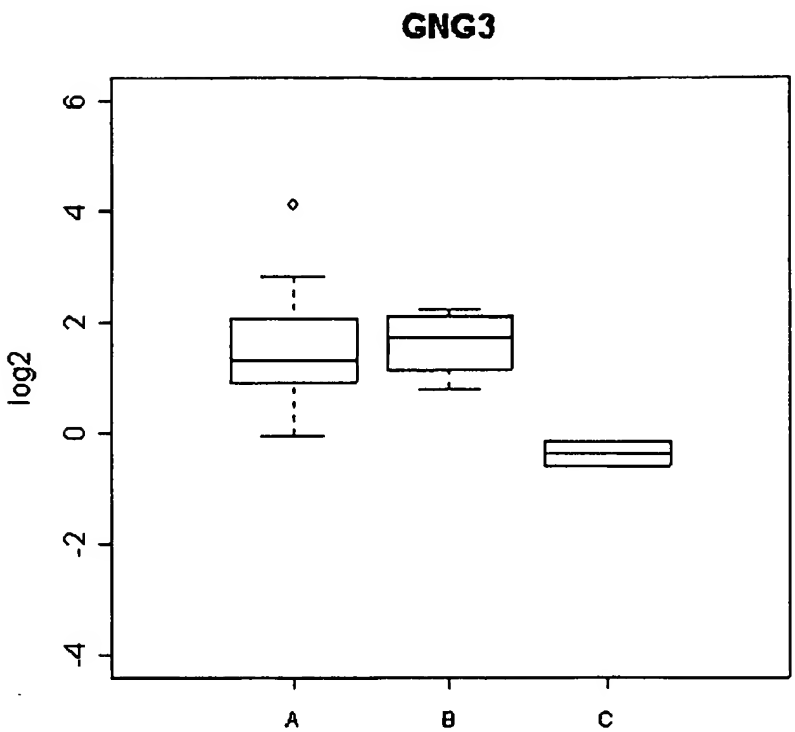
[Fig. 089]



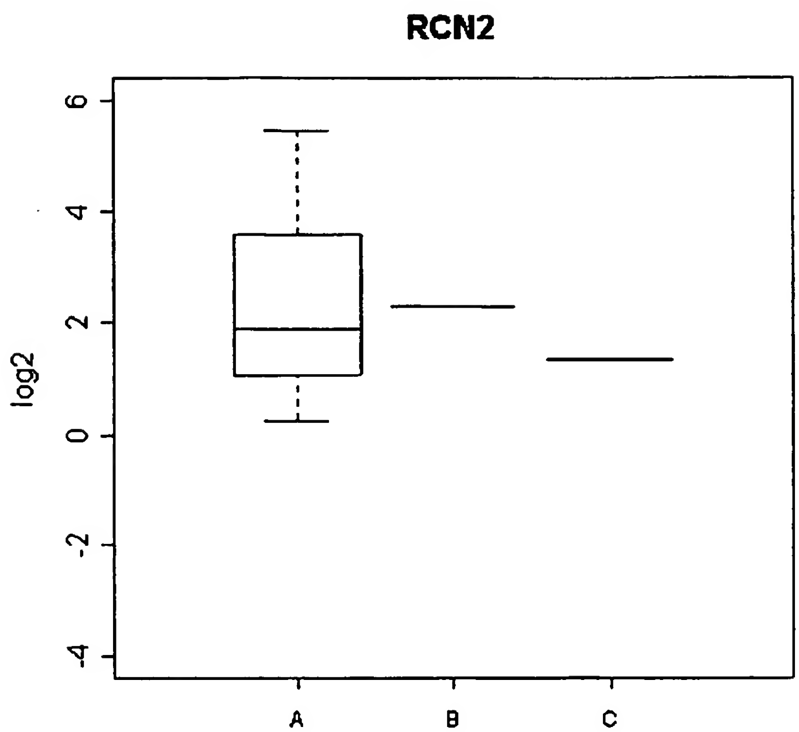
[Fig. 090]



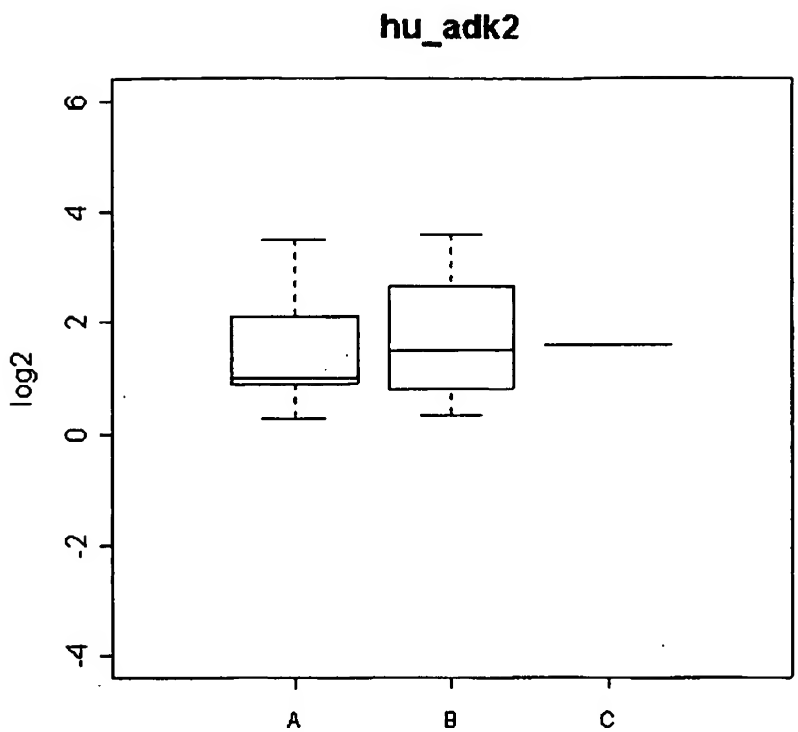
[Fig. 091]



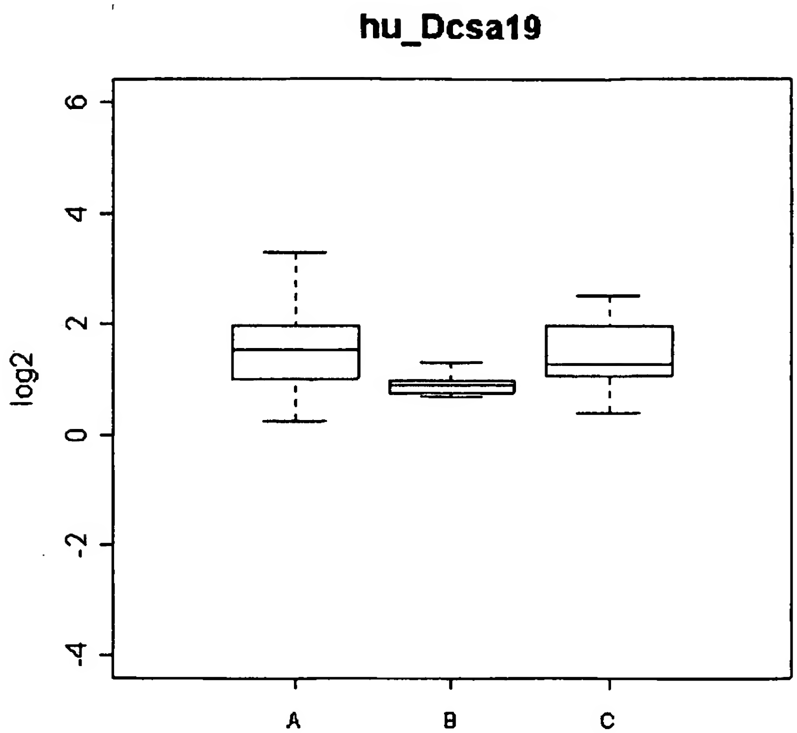
[Fig. 092]



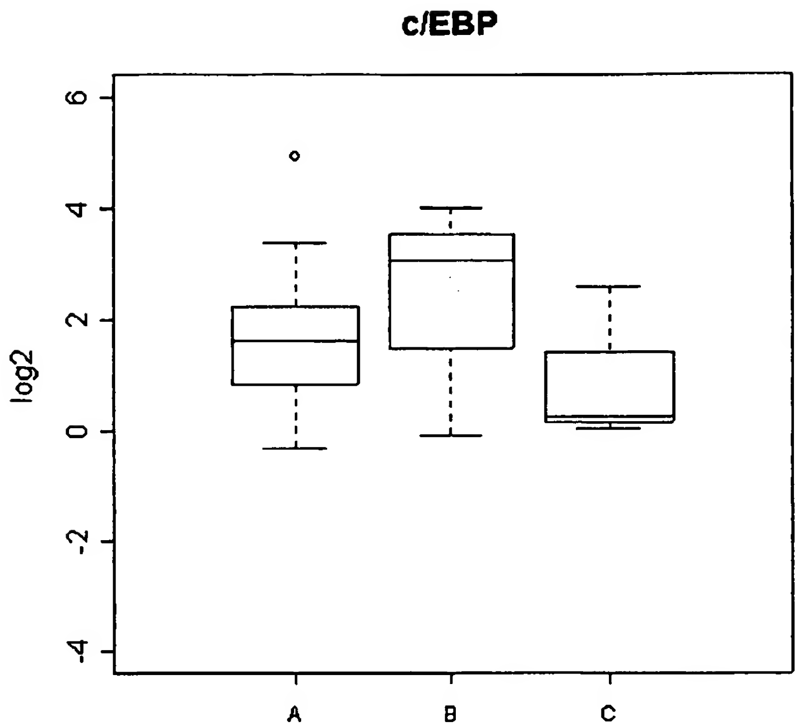
[Fig. 093]



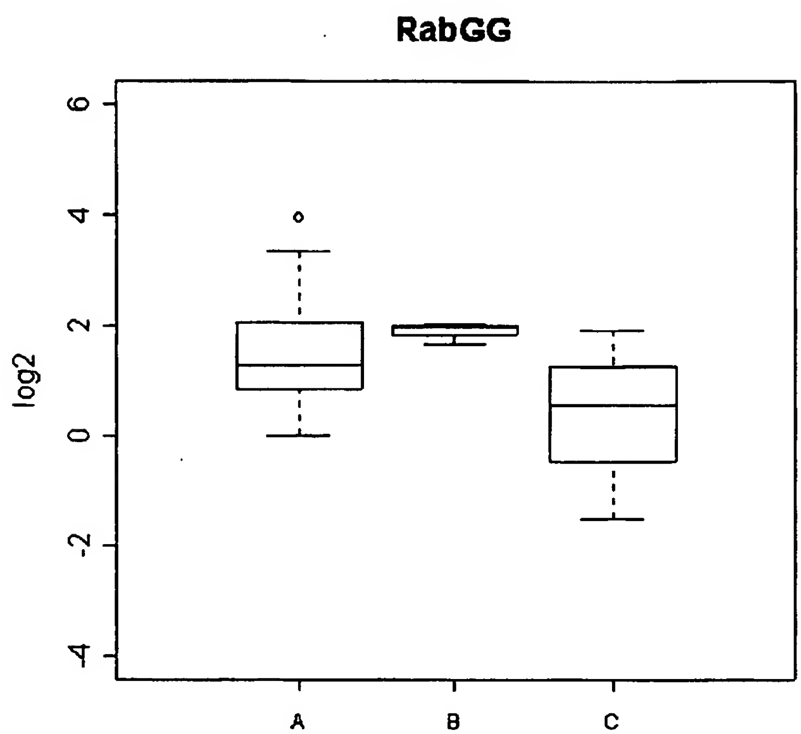
[Fig. 094]



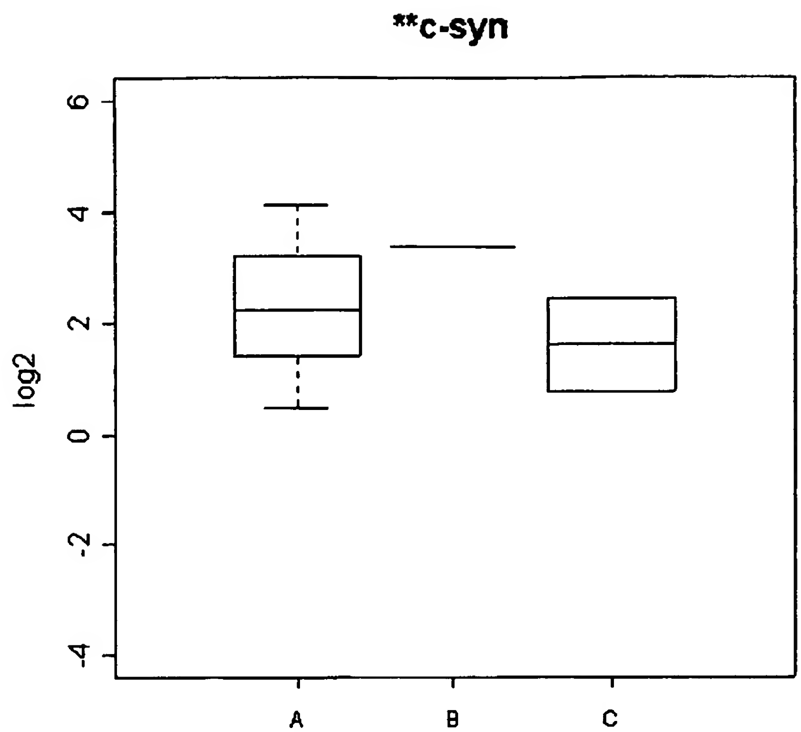
[Fig. 095]



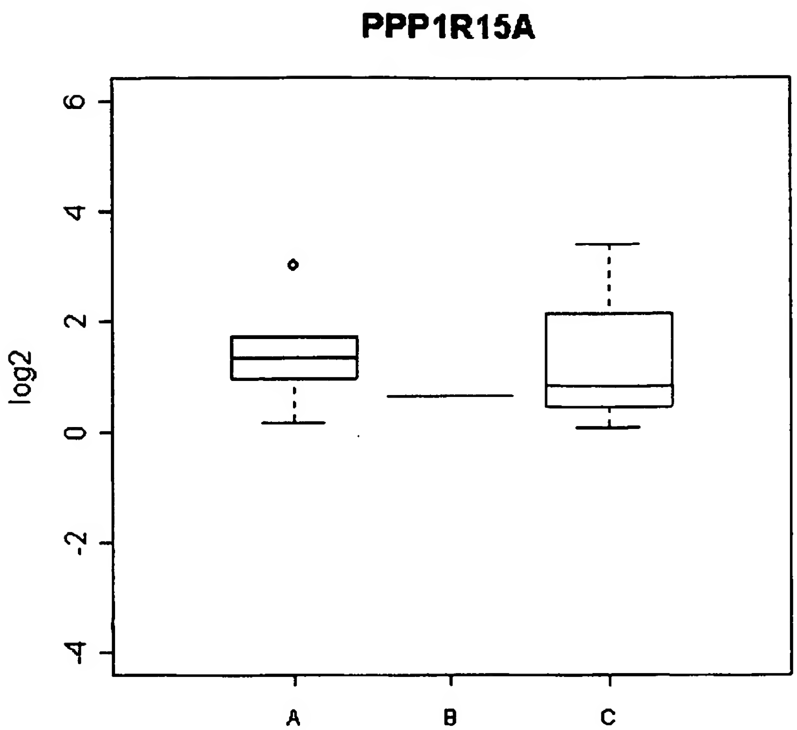
[Fig. 096]



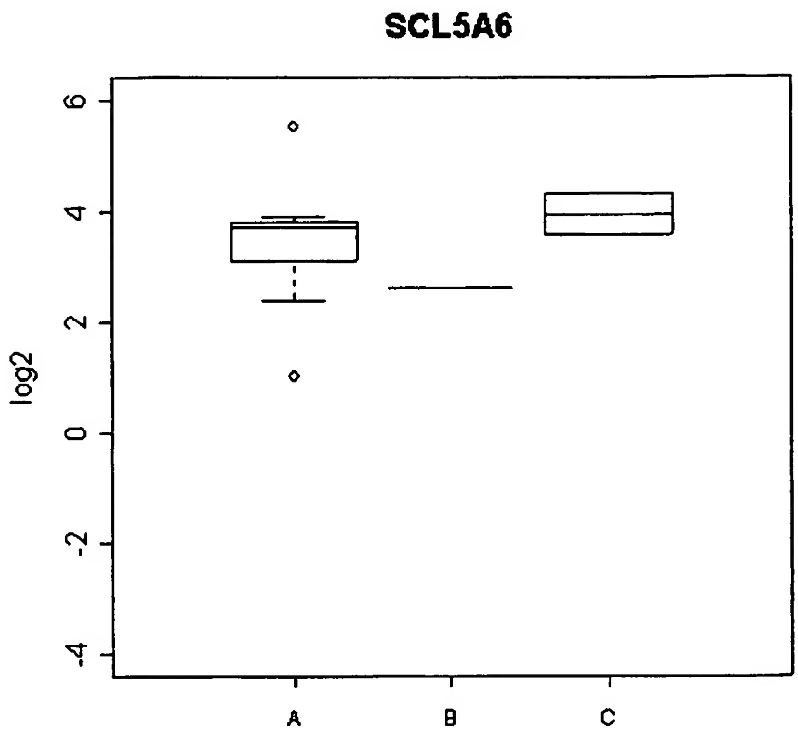
[Fig. 097]



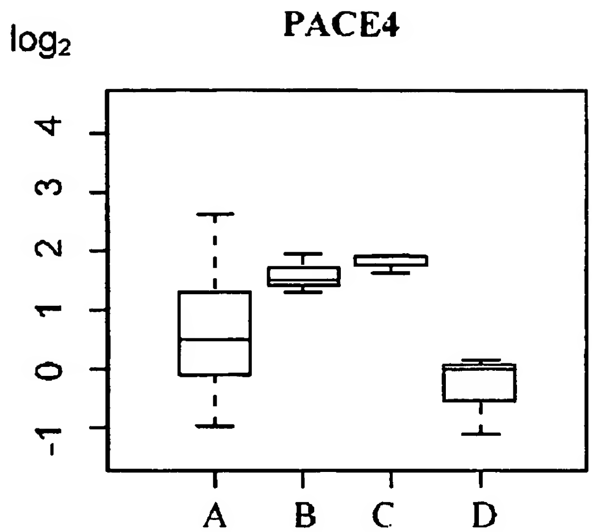
[Fig. 098]

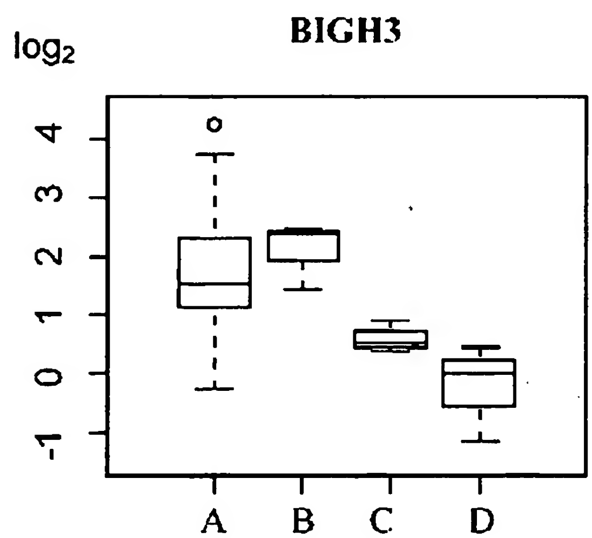


[Fig. 099]

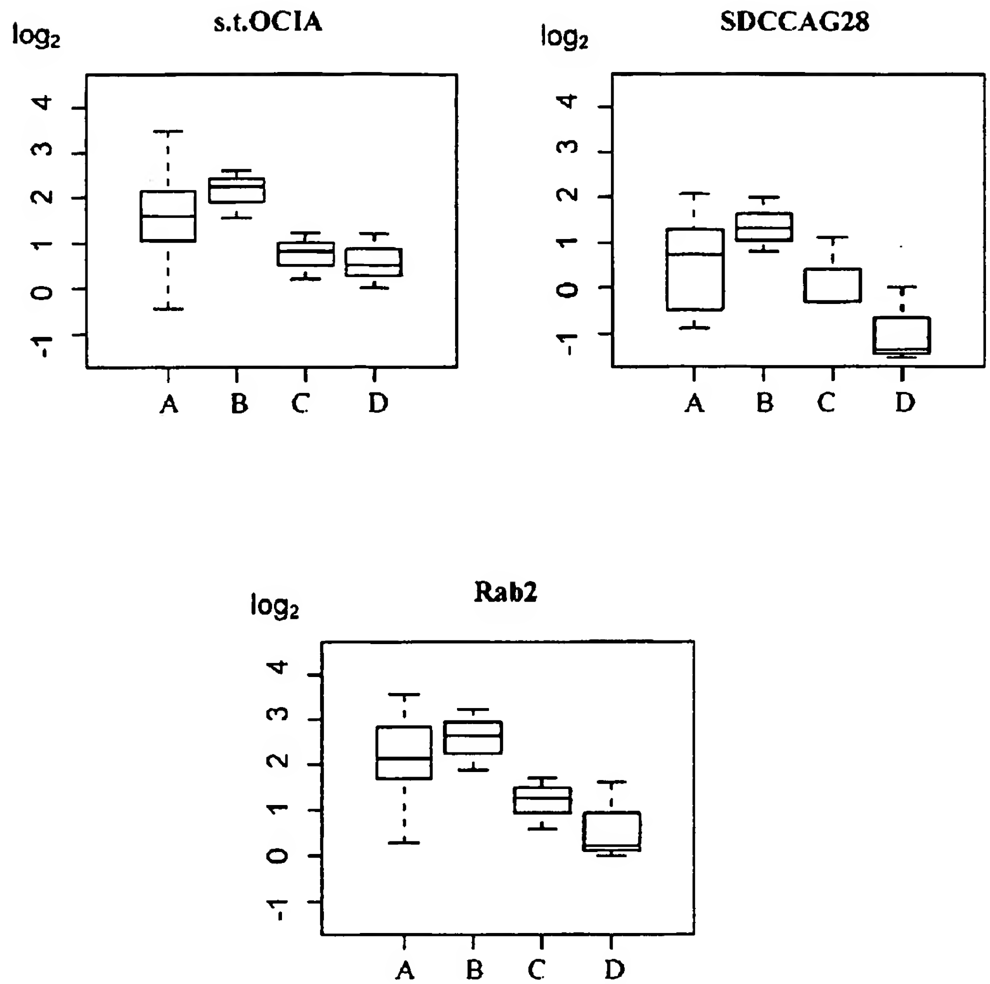


[Fig. 100]





[Fig. 101]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2
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0
-1
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log2
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4
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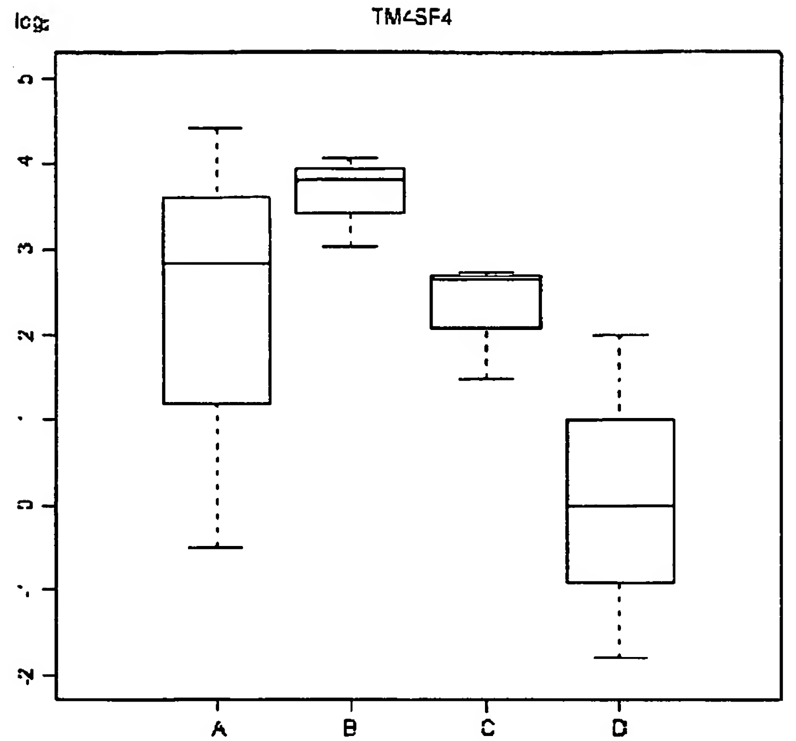
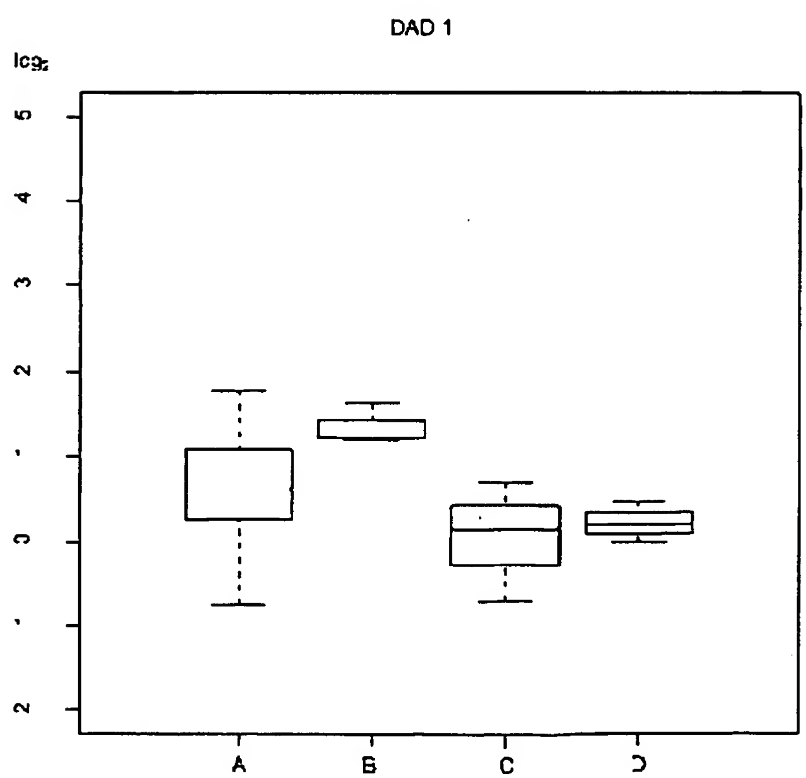
2
1
0
-1
A B C D

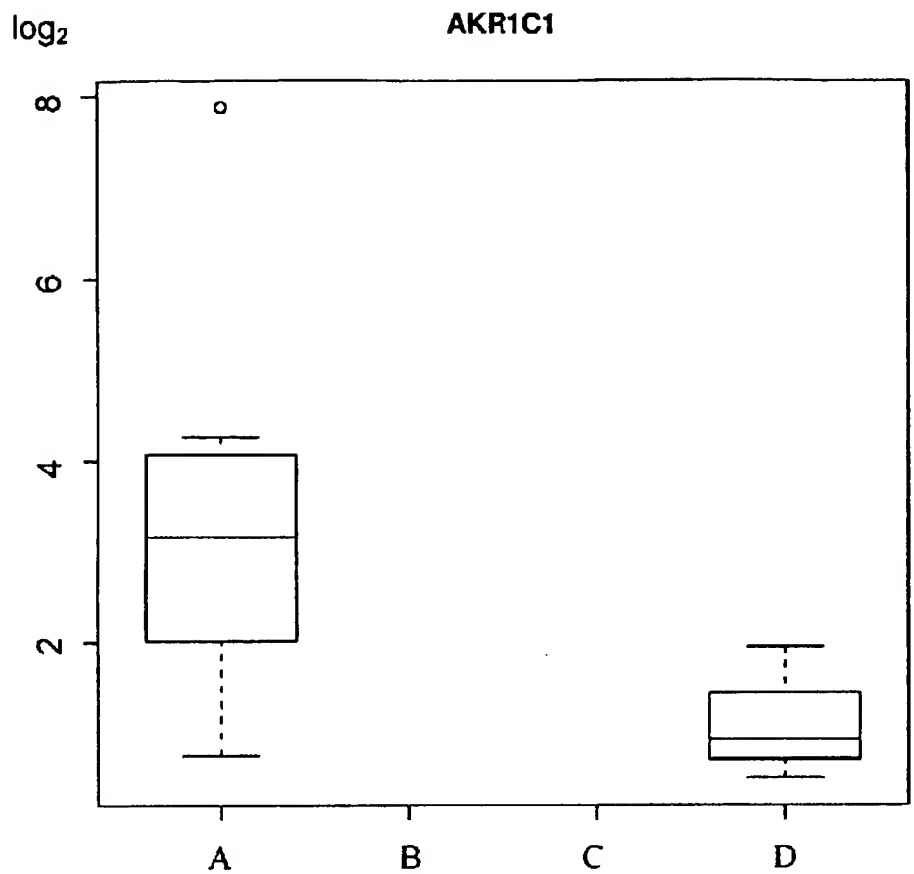
[Fig. 102]



[Fig. 103]

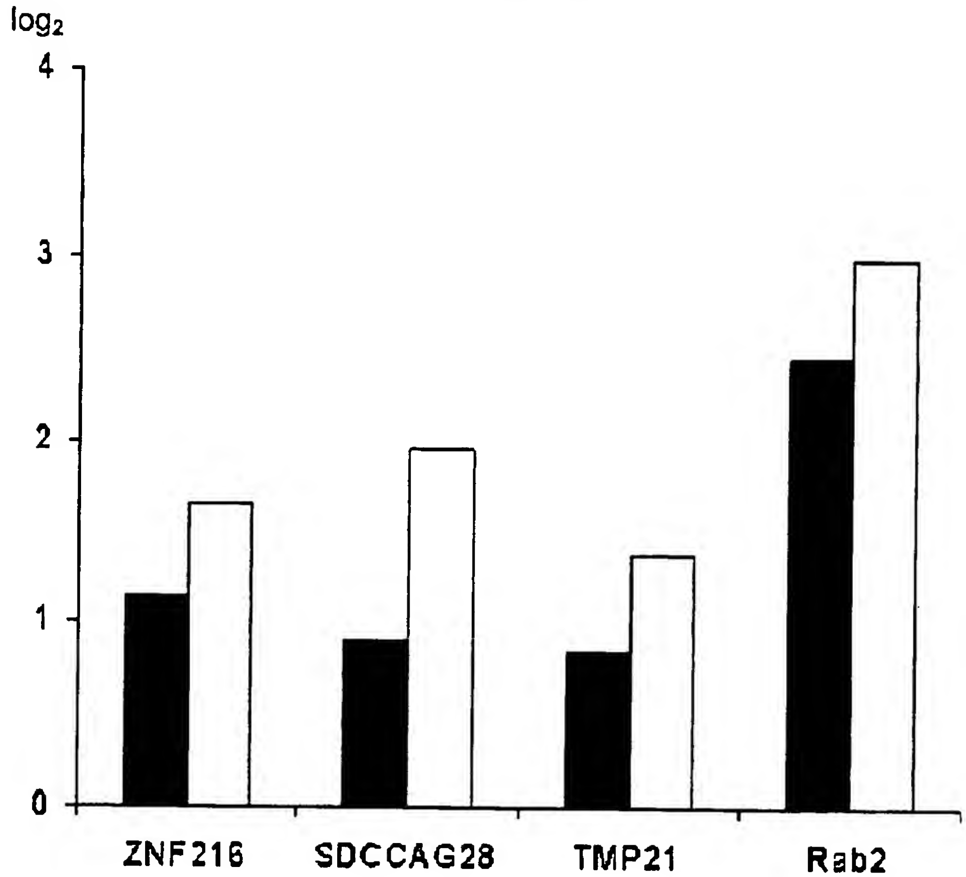


[Fig. 104]

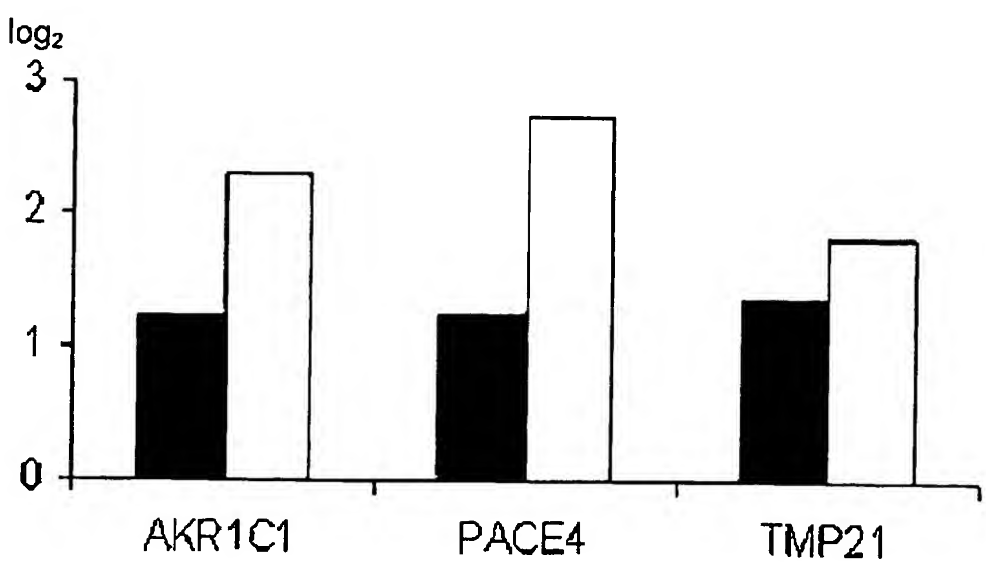


[Fig. 105]

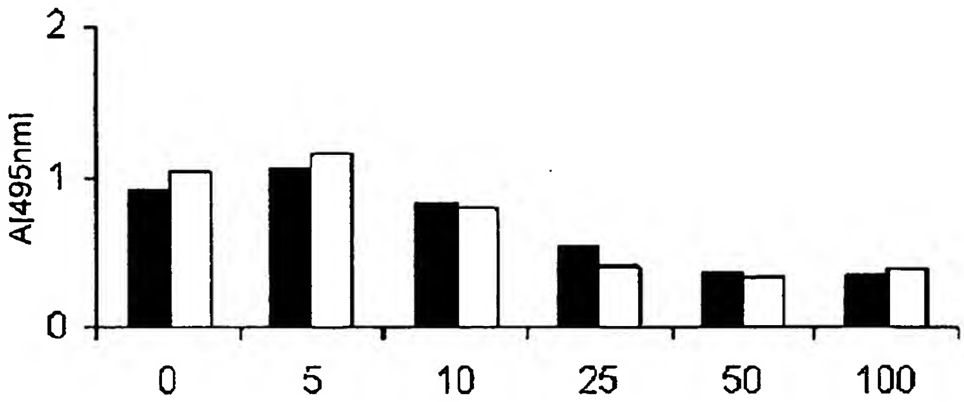
[Fig. 106]



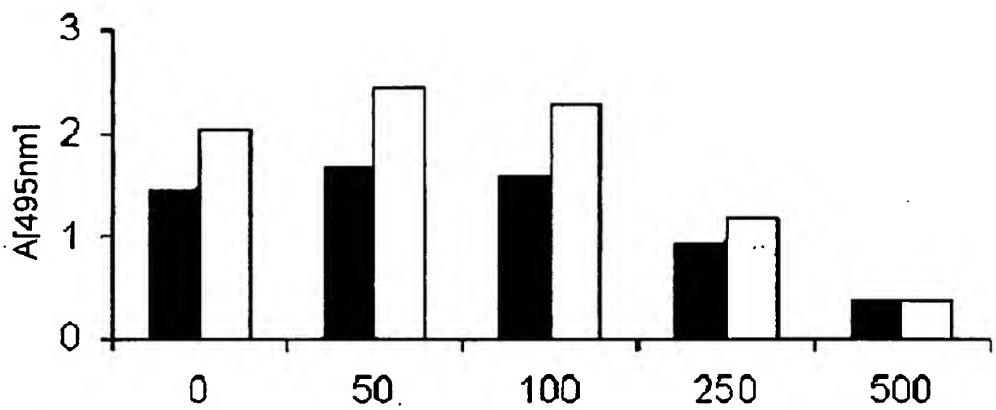
[Fig. 107]



[Fig. 108]



[Fig. 109]



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212> DNA
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1920

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2100

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eolf-seql-S000001.txt

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7860

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7920

aaaaaaaaa aaaaaaaaaa a
7941

210> 26
211> 1530
212> DNA
213> Homo sapiens

400> 26
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120

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1260

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1380

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1440

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1500

aaaaaaaaa aaaaaaaaaa aaaaaaaaaa
1530

210> 27
211> 2314

eolf-seql-S000001.txt

:212> DNA
:213> Homo sapiens

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2314

210> 28
211> 2848
212> DNA
213> Homo sapiens

400> 28
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211> 2424

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:213> Homo sapiens

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420

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eolf-seql-S000001.txt

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13> Homo sapiens

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12> DNA
13> Homo sapiens

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1777

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11> 1336
12> DNA
13> Homo sapiens

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1320

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1336

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11> 1414
12> DNA
13> Homo sapiens

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:10> 74
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:13> Homo sapiens

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aaaaaaaa aaaaaaaaa
3080

10> 75
11> 2181
12> DNA
13> Homo sapiens

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12> DNA
13> Homo sapiens

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13> Homo sapiens

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10> 79
11> 1124
12> DNA
13> Homo sapiens

00> 79
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1020

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1080

taaacaaa taaaatactt tttatcacaa aaaaaaaaaa aaaa
1124

10> 80
11> 1867
12> DNA
13> Homo sapiens

00> 80

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aaaaa
1867

10> 81
11> 3236
12> DNA
13> Homo sapiens

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3236

10> 82
11> 787
12> DNA
13> Homo sapiens

00> 82
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780

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787

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11> 912
12> DNA
13> Homo sapiens

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900

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10> 84
11> 1700
12> DNA
13> Homo sapiens

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10> 85
11> 961
12> DNA
13> Homo sapiens

00> 85
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960

961

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11> 700
12> DNA
13> Homo sapiens

00> 86
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10> 87
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12> DNA
13> Homo sapiens

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1740

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2880

eolf-seql-S000001.txt
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3120

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3660

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3720

ctttggaa caatgaaaaa aaaaaaaaaa
3750

10> 88
11> 1526
12> DNA
13> Homo sapiens

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1080

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eolf-seql-S000001.txt

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1320

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1440

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1500

aaaaaaaa aaaaaaaaaa aaaaaa
1526

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<211> 2650
<212> DNA
<213> Homo sapiens

<400> 89
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60

aggagggg gctgccgcgg gcgaggagga ggggtcgccg cgagccgaag gccttcgaga
120

cgcccgcc gcccggcggc gagagtagag gcgaggttgt tgtgcgagcg gcgcgtcctc
180

ccgcccgg gcgcgccgcg cttctcccag cgcaccgagg accgcccggg cgcacacaaa
240

cgccgccc gcgccgcacc gcccggcggc cgccgcccgc gccagggagg gattcggccg
300

gggccggg gacaccccgg cgccgccccc tcggtgctct cggaaggccc accggctccc
360

gcccgccg gggacccccc ggagccgcct cggccgcgcc ggaggagggc ggggagagga
420

atgtgagt gggctccgga gcctcagcgc cgcgcagttt ttttgaagaa gcaggatgct
480

tctaaacg tggaaaaaga ccagtcctgc ctctgttgta gaagacatgt ggtgtatata
540

gtttgtga tcgttggcgg acattttgga atttagataa tgggctgtgt gcaatgtaag

600

taaagaag caacaaaact gacggaggag agggacggca gcctgaacca gagctctggg
660

ccgctatg gcacagaccc cacccctcag cactacccca gcttcggtgt gacctccatc
720

caactaca acaacttcca cgcagccggg ggccaaggac tcaccgtctt tggaggtgtg
780

ctcttcgt ctcatacggg gaccttgcgt acgagaggag gaacaggagt gacactcttt
840

ggcccttt atgactatga agcacggaca gaagatgacc tgagttttca caaaggagaa
900

atttcaaa tattgaacag ctcggaagga gattggtggg aagcccgctc cttgacaact
960

agagacag gttacattcc cagcaattat gtggctccag ttgactctat ccaggcagaa
1020

gtggtact ttggaaaact tggccgaaaa gatgctgagc gacagctatt gtcctttgga
1080

cccaagag gtacctttct tatccgcgag agtgaaacca ccaaaggtgc ctattcactt
1140

tatccgtg attgggatga tatgaaagga gaccatgtca aacattataa aattcgcaaa
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tgacaatg gtggatacta cattaccacc cgggcccagt ttgaaacact tcagcagctt
1260

acaacatt actcagagag agctgcaggt ctctgctgcc gcctagtagt tccctgtcac
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1380

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1440

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1500

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1800

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1920

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1980

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2100

ıagaacgcc ccacttttga gtacttgcag agcttcctgg aagactactt taccgcgaca
2160

ıgccccagt accaacctgg tgaaaacctg taaggcccgg gtctgcggag agaggccttg
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2400

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ctgttcag tgtaaatagt tactccagtg ccaacaatcc tagtgctttc ctttttttaaa
2520

.tgcaaatc ctatgtgatt ttaactctgt cttcacctga ttcaactaaa aaaaaaaaag
2580

ttattttc caaaagtggc ctctttgtct aaaacaataa aatttttttt catgttttaa
2640

aaaaccaa
2650

10> 90
11> 2073

eolf-seql-S000001.txt

:12> DNA
:13> Homo sapiens

100> 90
ıatttagat aatgggctgt gtgcaatgta aggataaaga agcaacaaaa ctgacggagg 60

jagggacgg cagcctgaac cagagctctg ggtaccgcta tggcacagac cccacccctc 120

jcactaccc cagcttcggt gtgacctcca tccccaacta caacaacttc cacgcagccg 180

jggccaagg actcaccgtc tttggaggtg tgaactcttc gtctcatacg gggaccttgc 240

:acgagagg aggaacagga gtgacactct ttgtggccct ttatgactat gaagcacgga 300

ıgaagatga cctgagtttt cacaaaggag aaaaatttca aatattgaac agctcggaag 360

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cgggccca gtttgaaaca cttcagcagc ttgtacaaca ttactcagag aaagctgatg 720

ttgtgttt taacttaact gtgattgcat cgagttgtac cccacaaact tctggattgg 780

aaagatgc ttgggaagtt gcacgtcgtt cgttgtgtct ggagaagaag ctgggtcagg 840

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cttaaacc aggcacaatg tcccccgaat cattccttga ggaagcgcag atcatgaaga 960

ctgaagca cgacaagctg gtccagctct atgcagtggt gtctgaggag cccatctaca 1020

eolf-seql-S000001.txt

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1080

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1140

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1200

:ggactcat atgcaagatt gctgacttcg gattggcccg attgatagaa gacaatgagt
1260

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1320

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1920

ctagtgct ttcctttttt aaaaatgcaa atcctatgtg attttaactc tgtcttcacc
1980

attcaact aaaaaaaaaa aagtattatt ttccaaaagt ggcctctttg tctaaaacaa
2040

aaattttt tttcatgttt taacaaaaac caa
2073

eolf-seql-S000001.txt

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:11> 2000
:12> DNA
:13> Homo sapiens

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agtgacac tctttgtggc cctttatgac tatgaagcac ggacagaaga tgacctgagt 360

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tatccagg cagaagagtg gtactttgga aaacttggcc gaaaagatgc tgagcgacag 540

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taaaattc gcaaacttga caatggtgga tactacatta ccacccgggc ccagtttgaa 720

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1020

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1080

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1140

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1200

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1380

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1680

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1800

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1980

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2000

10> 92

:11> 2349
:12> DNA
:13> Homo sapiens

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600

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900

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960

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1020

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1080

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1200

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1320

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1380

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1440

aagatgagg acagtgatac aggatcagcc gaggatgaaa gagaagctga gacttctgct
1500

ccacacccc ctgcaagtgc tttcttgaag gcctgggtgt atcggccagg agaggacacg
1560

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1620

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1680

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1740

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1800

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ctgggagc agcttgctcg ggatcgcagc cgcttcgcac gccgcatcgc ccaggcccag
2040

ggagctga gcccctgcct cacccctgct gcccgggcca gagcctgggc acgcctcagg
2100

ıcccacctt tagccccccat ccctgccctc acccagacct tgccttcctc ctctgtccct
2160

:gtccccag tccagaccac gcccttgagc caagctgtgg ctacaccttc ccgctcctct
2220

:tgctgcag cggctgccct ggacctcagt gggaggcgtg gctgagacca actggtttgc
2280

.ataattta ttaactattt attttttcta agtgtgggtt tatataagga ataaagcctt
2340

.gatttgt
2349

10> 93
11> 3162
12> DNA
13> Homo sapiens

00> 93
gccctagc cctctttcgg ggatactggc cgacccccctc ttccttttcc cctttagtga
60

gcctcccc cgtcgccgcg cggcttcccg gagccgactg cagactccct cagcccggtg
120

ccccgcgt ccggacgccg aggtcgcggc ttcgcagaaa ctcgggcccc tccatccgcc
180

cagaaaag ggagcgatgt tgatctcagg aagcacaaag ggaccttcct agctctgact
240

accacgga gctcaccctg gacagtatca ctccgtggag gaagactgtg agactgtggc
300

gaagccag attgtagcca cacatccgcc cctgccctac cccagagccc tggagcagca
360

tggctgca gatcacagac acagtgagga tatgagtgta ggggtgagca cctcagcccc
420

tttcccca acctcgggca caagcgtggg catgtctacc ttctccatca tggactatgt
480

tgttcgtc ctgctgctgg ttctctctct tgccattggg ctctaccatg cttgtcgtgg
540

gggccgg catactgttg gtgagctgct gatggcggac cgcaaaatgg gctgccttcc
600

tggcactg tccctgctgg ccaccttcca gtcagccgtg gccatcctgg gtgtgccgtc
660

eolf-seql-S000001.txt
jagatctac cgatttggga cccaatattg gttcctgggc tgctgctact ttctggggct
720

:tgatacct gcacacatct tcatccccgt tttctaccgc ctgcatctca ccagtgccta
780

jagtacctg gagcttcgat tcaataaaac tgtgcgagtg tgtggaactg tgaccttcat
840

.ttcagatg gtgatctaca tgggagttgt gctctatgct ccgtcattgg ctctcaatgc
900

'tgactggc tttgatctgt ggctgtccgt gctggccctg ggcattgtct gtaccgtcta
960

.cagctctg ggtgggctga aggccgtcat ctggacagat gtgttccaga cactggtcat
1020

tcctcggg cagctggcag ttatcatcgt ggggtcagcc aaggtgggcg gcttggggcg
1080

'tgtgggcc gtggcttccc agcacggccg catctctggg tttgagctgg atccagaccc
1140

ttgtgcgg cacaccttct ggaccttggc cttcgggggt gtcttcatga tgctctcctt
1200

acggggtg aaccaggctc aggtgcagcg gtacctcagt tcccgcacgg agaaggctgc
1260

tgctctcc tgttatgcag tgttcccctt ccagcaggtg tccctctgcg tgggctgcct
1320

ttggcctg gtcatgttcg cgtattacca ggagtatccc atgagcattc agcaggctca
1380

cagcccca gaccagttcg tcctgtactt tgtgatggat ctcctgaagg gcctgccagg
1440

tgccaggg ctcttcattg cctgcctctt cagcggctct ctcagcacta tatcctctgc
1500

ttaattca ttggcaactg ttacgatgga agacctgatt cgaccttggt tccctgagtt
1560

ctgaagcc cgggccatca tgctttccag aggccttgcc tttggctatg ggctgctttg
1620

taggaatg gcctatattt cctcccagat gggacctgtg ctgcaggcag caatcagcat
1680

ttggcatg gttgggggac cgctgctggg actcttctgc cttggaatgt tctttccatg
1740

:taaccct cctggtgctg ttgtgggcct gttggctggg ctcgtcatgg ccttctggat

1800

gcatcggg agcatcgtga ccagcatggg cttcagcatg ccaccctctc cctctaatgg
1860

ccagcttc tccctgccca ccaatctaac cgttgccact gtgaccacac tgatgccctt
1920

ctaccttc tccaagccca cagggctgca gcggttctat tccttgtctt acttatggta
1980

gtgctcac aactccacca cagtgattgt ggtgggcctg attgtcagtc tactcactgg
2040

gaatgcga ggccggtccc tgaaccctgc aaccatttac ccagtgttgc caaagctcct
2100

ccctcctt ccgttgtcct gtcagaagcg gctccactgc aggagctacg gccaggacca
2160

tcgacact ggcctgtttc ctgagaagcc gaggaatggt gtgctggggg acagcagaga
2220

aggaggcc atggccctgg atggcacagc ctatcagggg agcagctcca cctgcatcct
2280

aggagacc tccctgtgat gttgactcag gaccccgcct ctgtcctcac tgtgccaggc
2340

tagccaga ggccaccctg tagtacaggg atgagtcttg gtgtgttctg cagggacagg
2400

tggatgat ctagctcata ccaaaggacc ttgttctgag aggttcttgc ctgcaggaga
2460

ctgtcaca tctcaagcat gtgaggcacc gtttttctcg tcgcttgcca atctgttttt
2520

aaggatca ggctcgtagg gagcaggatc atgccagaaa tagggatgga agtgcatcct
2580

gggaaaaa gataatggct tctgattcaa catagccata gtcctttgaa gtaagtggct
2640

aaacagca ctctggttat aattgcccca gggcctgatt caggactgac tctccaccat
2700

aactggaa gctgcttccc ctgtagtccc catttcagta ccagttctgc cagccacagt
2760

gcccctat tattactttc agattgtctg tgacactcaa gcccctctca tttttatctg
2820

tacctcca ttctgaagag ggaggttttg gtgtccctgg tcctctggga atagaagatc
2880

ıtttgtctt tgtgtagagc aagcacgttt tccacctcac tgtctccatc ctccacctct
2940

ıgatggaca cttaagagac ggggcaaatg tggatccaag aaaccagggc catgaccagg
3000

:cactgtgg agcagccatc tatctacctg actcctgagc caggctgccg tggtgtcatt
3060

:tgtcatcc gtgctctgtt tccttttgga gtttcttctc cacattatct ttgttcctgg
3120

jaataaaaa ctaccattgg acctaaaaa aaaaaaaaaa aa
3162

:10> 94
:11> 20
:12> DNA
:13> Homo sapiens

!00> 94
:acatcgct cagacaccat
20

:10> 95
:11> 17
:12> DNA
:13> Homo sapiens

00> 95
:caggcgcc caatacg
17

10> 96
11> 28
12> DNA
13> Homo sapiens

00> 96
aatccgtt gactccgacc ttcacctt
28

10> 97
11> 20
12> DNA
13> Homo sapiens

00> 97
ggccaacc gcgagaagat
20

?10> 98
?11> 20
?12> DNA
?13> Homo sapiens

ł00> 98
:caccggag tccatcacga
20

:10> 99
:11> 32
:12> DNA
:13> Homo sapiens

:00> 99
:atgtacgt tgctatccag gctgtgctat cc
32

:10> 100
11> 25
12> DNA
13> Homo sapiens

00> 100
.actgggac gacatggaga aaatc
25

10> 101
11> 22
12> DNA
13> Homo sapiens

00> 101
tggctggg gtgttgaagg tc
22

10> 102
11> 21
12> DNA
13> Homo sapiens

00> 102
gaggacaa aataactacc c
21

10> 103
11> 22
12> DNA

eolf-seql-S000001.txt

```
!13>  Homo sapiens

!00>  103
ıattcagga gctttttctt ca
   22


!10>  104
!11>  22
!12>  DNA
!13>  Homo sapiens

!00>  104
ıattcagga gctttttctt ca
   22


:10>  105
:11>  32
:12>  DNA
:13>  Homo sapiens

:00>  105
.ctgggctg agaaactgat ggactgggct ga
   32


 10>  106
 11>  23
 12>  DNA
 13>  Homo sapiens

 00>  106
 ggaaaggt cactgaaaaa tct
   23


 10>  107
 11>  21
 12>  PRT
 13>  Homo sapiens

 00>  107

 y Cys Thr Gly Gly Cys Thr Gly Cys Gly Gly Thr Thr Gly Ala Ala
                 5                   10                  15


 y Thr Thr Gly Gly
             20


 10>  108
 11>  17
 12>  DNA
```

:13> Homo sapiens

:00> 108
:gcgggcta cgacctg
17

:10> 109
:11> 20
.12> DNA
13> Homo sapiens

00> 109
'ccactctt ccataacacc
20

10> 110
11> 32
12> DNA
13> Homo sapiens

00> 110
tccgtttt cacaacagct ttctccatag gt
32

10> 111
11> 16
12> DNA
13> Homo sapiens

00> 111
aaaacgac ggccag
16

10> 112
11> 17
12> DNA
13> Homo sapiens

00> 112
ggaaacag ctatgac
17

10> 113
11> 479
12> PRT
13> Homo sapiens

)0> 113

: Asp Glu Thr Ser Pro Leu Val Ser Pro Glu Arg Ala Gln Pro Pro

eolf-seql-S000001.txt

```
                5                   10                  15

;p Tyr Thr Phe Pro Ser Gly Ser Gly Ala His Phe Pro Gln Val Pro
           20                  25                  30

.y Gly Ala Val Arg Val Ala Ala Ala Ala Gly Ser Gly Pro Ser Pro
       35                  40                  45

:o Gly Ser Pro Gly His Asp Arg Glu Arg Gln Pro Leu Leu Asp Arg
   50                  55                  60

.a Arg Gly Ala Ala Ala Gln Gly Gln Thr Gln Thr Val Ala Ala Gln
'                  70                  75                  80

.a Gln Ala Leu Ala Ala Gln Ala Ala Ala Ala Ala His Ala Ala Gln
               85                  90                  95

a His Arg Glu Arg Asn Glu Phe Pro Glu Asp Pro Glu Phe Glu Ala
           100                 105                 110

.l Val Arg Gln Ala Glu Leu Ala Ile Glu Arg Cys Ile Phe Pro Glu
       115                 120                 125

g Ile Tyr Gln Gly Ser Ser Gly Ser Tyr Phe Val Lys Asp Pro Gln
  130                 135                 140

y Arg Ile Ile Ala Val Phe Lys Pro Lys Asn Glu Glu Pro Tyr Gly
5                 150                 155                 160

s Leu Asn Pro Lys Trp Thr Lys Trp Leu Gln Lys Leu Cys Cys Pro
               165                 170                 175

s Cys Phe Gly Arg Asp Cys Leu Val Leu Asn Gln Gly Tyr Leu Ser
           180                 185                 190

u Ala Gly Ala Ser Leu Val Asp Gln Lys Leu Glu Leu Asn Ile Val
       195                 200                 205

ɔ Arg Thr Lys Val Val Tyr Leu Ala Ser Glu Thr Phe Asn Tyr Ser
  210                 215                 220
```

```
La Ile Asp Arg Val Lys Ser Arg Gly Lys Arg Leu Ala Leu Glu Lys
25                 230                 235                 240

al Pro Lys Val Gly Gln Arg Phe Asn Arg Ile Gly Leu Pro Pro Lys
               245                 250                 255

al Gly Ser Phe Gln Leu Phe Val Glu Gly Tyr Lys Asp Ala Asp Tyr
            260                 265                 270

rp Leu Arg Arg Phe Glu Ala Glu Pro Leu Pro Glu Asn Thr Asn Arg
        275                 280                 285

.n Leu Leu Leu Gln Phe Glu Arg Leu Val Val Leu Asp Tyr Ile Ile
    290                 295                 300

:g Asn Thr Asp Arg Gly Asn Asp Asn Trp Leu Ile Lys Tyr Asp Cys
)5                 310                 315                 320

:o Met Asp Ser Ser Ser Ser Arg Asp Thr Asp Trp Val Val Val Lys
               325                 330                 335

.u Pro Val Ile Lys Val Ala Ala Ile Asp Asn Gly Leu Ala Phe Pro
            340                 345                 350

:u Lys His Pro Asp Ser Trp Arg Ala Tyr Pro Phe Tyr Trp Ala Trp
        355                 360                 365

u Pro Gln Ala Lys Val Pro Phe Ser Gln Glu Ile Lys Asp Leu Ile
    370                 375                 380

u Pro Lys Ile Ser Asp Pro Asn Phe Val Lys Asp Leu Glu Glu Asp
5                  390                 395                 400

u Tyr Glu Leu Phe Lys Lys Asp Pro Gly Phe Asp Arg Gly Gln Phe
               405                 410                 415

s Lys Gln Ile Ala Val Met Arg Gly Gln Ile Leu Asn Leu Thr Gln
            420                 425                 430

a Leu Lys Asp Asn Lys Ser Pro Leu His Leu Val Gln Met Pro Pro
        435                 440                 445
```

al Ile Val Glu Thr Ala Arg Ser His Gln Arg Ser Ser Ser Glu Ser
450 455 460

yr Thr Gln Ser Phe Gln Ser Arg Lys Pro Phe Phe Ser Trp Trp
55 470 475

210> 114
211> 213
212> PRT
213> Homo sapiens

400> 114

et Ala Gln Glu Thr Asn Gln Thr Pro Gly Pro Met Leu Cys Ser Thr
5 10 15

.y Cys Gly Phe Tyr Gly Asn Pro Arg Thr Asn Gly Met Cys Ser Val
20 25 30

's Tyr Lys Glu His Leu Gln Arg Gln Gln Asn Ser Gly Arg Met Ser
35 40 45

:o Met Gly Thr Ala Ser Gly Ser Asn Ser Pro Thr Ser Asp Ser Ala
50 55 60

:r Val Gln Arg Ala Asp Thr Ser Leu Asn Asn Cys Glu Gly Ala Ala
70 75 80

.y Ser Thr Ser Glu Lys Ser Arg Asn Val Pro Val Ala Ala Leu Pro
85 90 95

.l Thr Gln Gln Met Thr Glu Met Ser Ile Ser Arg Glu Asp Lys Ile
100 105 110

.r Thr Pro Lys Thr Glu Val Ser Glu Pro Val Val Thr Gln Pro Ser
115 120 125

o Ser Val Ser Gln Pro Ser Thr Ser Gln Ser Glu Glu Lys Ala Pro
130 135 140

u Leu Pro Lys Pro Lys Lys Asn Arg Cys Phe Met Cys Arg Lys Lys
5 150 155 160

eolf-seql-S000001.txt

al Gly Leu Thr Gly Phe Asp Cys Arg Cys Gly Asn Leu Phe Cys Gly
165 170 175

eu His Arg Tyr Ser Asp Lys His Asn Cys Pro Tyr Asp Tyr Lys Ala
180 185 190

lu Ala Ala Ala Lys Ile Arg Lys Glu Asn Pro Val Val Val Ala Glu
195 200 205

ys Ile Gln Arg Ile
210

210> 115
211> 323
212> PRT
213> Homo sapiens

400> 115

et Asp Ser Lys Tyr Gln Cys Val Lys Leu Asn Asp Gly His Phe Met
5 10 15

ro Val Leu Gly Phe Gly Thr Tyr Ala Pro Ala Glu Val Pro Lys Ser
20 25 30

ys Ala Leu Glu Ala Thr Lys Leu Ala Ile Glu Ala Gly Phe Arg His
35 40 45

e Asp Ser Ala His Leu Tyr Asn Asn Glu Glu Gln Val Gly Leu Ala
50 55 60

e Arg Ser Lys Ile Ala Asp Gly Ser Val Lys Arg Glu Asp Ile Phe
70 75 80

r Thr Ser Lys Leu Trp Cys Asn Ser His Arg Pro Glu Leu Val Arg
85 90 95

o Ala Leu Glu Arg Ser Leu Lys Asn Leu Gln Leu Asp Tyr Val Asp
100 105 110

u Tyr Leu Ile His Phe Pro Val Ser Val Lys Pro Gly Glu Glu Val
115 120 125

```
e Pro Lys Asp Glu Asn Gly Lys Ile Leu Phe Asp Thr Val Asp Leu
  130                     135                     140

s Ala Thr Trp Glu Ala Val Glu Lys Cys Lys Asp Ala Gly Leu Ala
5                     150                     155                 160

s Ser Ile Gly Val Ser Asn Phe Asn Arg Arg Gln Leu Glu Met Ile
                  165                     170                     175

u Asn Lys Pro Gly Leu Lys Tyr Lys Pro Val Cys Asn Gln Val Glu
              180                     185                     190

s His Pro Tyr Phe Asn Gln Arg Lys Leu Leu Asp Phe Cys Lys Ser
      195                     200                     205

s Asp Ile Val Leu Val Ala Tyr Ser Ala Leu Gly Ser His Arg Glu
  210                     215                     220

u Pro Trp Val Asp Pro Asn Ser Pro Val Leu Leu Glu Asp Pro Val
5                     230                     235                 240

u Cys Ala Leu Ala Lys Lys His Lys Arg Thr Pro Ala Leu Ile Ala
                  245                     250                     255

a Arg Tyr Gln Leu Gln Arg Gly Val Val Val Leu Ala Lys Ser Tyr
              260                     265                     270

n Glu Gln Arg Ile Arg Gln Asn Val Gln Val Phe Glu Phe Gln Leu
      275                     280                     285

r Ser Glu Glu Met Lys Ala Ile Asp Gly Leu Asn Arg Asn Val Arg
  290                     295                     300

r Leu Thr Leu Asp Ile Phe Ala Gly Pro Pro Asn Tyr Pro Phe Ser
5                     310                     315                 320

) Glu Tyr


.0>  116
.1>  164
```

eolf-seql-S000001.txt

12> PRT
13> Homo sapiens

00> 116

```
t Pro Cys Ser Glu Glu Thr Pro Ala Ile Ser Pro Ser Lys Arg Ala
              5                   10                  15

g Pro Ala Glu Val Gly Gly Met Gln Leu Arg Phe Ala Arg Leu Ser
          20                  25                  30

u His Ala Thr Ala Pro Thr Arg Gly Ser Ala Arg Ala Ala Gly Tyr
      35                  40                  45

p Leu Tyr Ser Ala Tyr Asp Tyr Thr Ile Pro Pro Met Glu Lys Ala
  50                  55                  60

l Val Lys Thr Asp Ile Gln Ile Ala Leu Pro Ser Gly Cys Tyr Gly
                  70                  75                  80

g Val Ala Pro Arg Ser Gly Leu Ala Ala Lys His Phe Ile Asp Val
              85                  90                  95

y Ala Gly Val Ile Asp Glu Asp Tyr Arg Gly Asn Val Gly Val Val
          100                 105                 110

u Phe Asn Phe Gly Lys Glu Lys Phe Glu Val Lys Lys Gly Asp Arg
      115                 120                 125

e Ala Gln Leu Ile Cys Glu Arg Ile Phe Tyr Pro Glu Ile Glu Glu
  130                 135                 140

l Gln Ala Leu Asp Asp Thr Glu Arg Gly Ser Gly Gly Phe Gly Ser
5                   150                 155                 160

r Gly Lys Asn
```

10> 117
11> 969
12> PRT
13> Homo sapiens

)0> 117

:t Pro Pro Arg Ala Pro Pro Ala Pro Gly Pro Arg Pro Pro Pro Arg
5 10 15

.a Ala Ala Ala Thr Asp Thr Ala Ala Gly Ala Gly Gly Ala Gly Gly
20 25 30

.a Gly Gly Ala Gly Gly Pro Gly Phe Arg Pro Leu Ala Pro Arg Pro
35 40 45

'p Arg Trp Leu Leu Leu Leu Ala Leu Pro Ala Ala Cys Ser Ala Pro
50 55 60

'o Pro Arg Pro Val Tyr Thr Asn His Trp Ala Val Gln Val Leu Gly
70 75 80

.y Pro Ala Glu Ala Asp Arg Val Ala Ala Ala His Gly Tyr Leu Asn
85 90 95

'u Gly Gln Ile Gly Asn Leu Glu Asp Tyr Tyr His Phe Tyr His Ser
100 105 110

's Thr Phe Lys Arg Ser Thr Leu Ser Ser Arg Gly Pro His Thr Phe
115 120 125

u Arg Met Asp Pro Gln Val Lys Trp Leu Gln Gln Gln Glu Val Lys
130 135 140

g Arg Val Lys Arg Gln Val Arg Ser Asp Pro Gln Ala Leu Tyr Phe
5 150 155 160

n Asp Pro Ile Trp Ser Asn Met Trp Tyr Leu His Cys Gly Asp Lys
165 170 175

n Ser Arg Cys Arg Ser Glu Met Asn Val Gln Ala Ala Trp Lys Arg
180 185 190

y Tyr Thr Gly Lys Asn Val Val Val Thr Ile Leu Asp Asp Gly Ile
195 200 205

u Arg Asn His Pro Asp Leu Ala Pro Asn Tyr Asp Ser Tyr Ala Ser
210 215 220

```
/r Asp Val Asn Gly Asn Asp Tyr Asp Pro Ser Pro Arg Tyr Asp Ala
25                 230                 235                 240

er Asn Glu Asn Lys His Gly Thr Arg Cys Ala Gly Glu Val Ala Ala
               245                 250                 255

er Ala Asn Asn Ser Tyr Cys Ile Val Gly Ile Ala Tyr Asn Ala Lys
           260                 265                 270

.e Gly Gly Ile Arg Met Leu Asp Gly Asp Val Thr Asp Val Val Glu
       275                 280                 285

.a Lys Ser Leu Gly Ile Arg Pro Asn Tyr Ile Asp Ile Tyr Ser Ala
   290                 295                 300

er Trp Gly Pro Asp Asp Asp Gly Lys Thr Val Asp Gly Pro Gly Arg
)5                 310                 315                 320

:u Ala Lys Gln Ala Phe Glu Tyr Gly Ile Lys Lys Gly Arg Gln Gly
               325                 330                 335

:u Gly Ser Ile Phe Val Trp Ala Ser Gly Asn Gly Gly Arg Glu Gly
           340                 345                 350

p Tyr Cys Ser Cys Asp Gly Tyr Thr Asn Ser Ile Tyr Thr Ile Ser
      355                 360                 365

l Ser Ser Ala Thr Glu Asn Gly Tyr Lys Pro Trp Tyr Leu Glu Glu
  370                 375                 380

s Ala Ser Thr Leu Ala Thr Thr Tyr Ser Ser Gly Ala Phe Tyr Glu
5                 390                 395                 400

g Lys Ile Val Thr Thr Asp Leu Arg Gln Arg Cys Thr Asp Gly His
              405                 410                 415

r Gly Thr Ser Val Ser Ala Pro Met Val Ala Gly Ile Ile Ala Leu
          420                 425                 430

a Leu Glu Ala Asn Ser Gln Leu Thr Trp Arg Asp Val Gln His Leu
```

435 440 445

:u Val Lys Thr Ser Arg Pro Ala His Leu Lys Ala Ser Asp Trp Lys
450 455 460

.l Asn Gly Ala Gly His Lys Val Ser His Phe Tyr Gly Phe Gly Leu
:5 470 475 480

.l Asp Ala Glu Ala Leu Val Val Glu Ala Lys Lys Trp Thr Ala Val
485 490 495

o Ser Gln His Met Cys Val Ala Ala Ser Asp Lys Arg Pro Arg Ser
500 505 510

e Pro Leu Val Gln Val Leu Arg Thr Thr Ala Leu Thr Ser Ala Cys
515 520 525

a Glu His Ser Asp Gln Arg Val Val Tyr Leu Glu His Val Val Val
530 535 540

g Thr Ser Ile Ser His Pro Arg Arg Gly Asp Leu Gln Ile Tyr Leu
5 550 555 560

l Ser Pro Ser Gly Thr Lys Ser Gln Leu Leu Ala Lys Arg Leu Leu
565 570 575

p Leu Ser Asn Glu Gly Phe Thr Asn Trp Glu Phe Met Thr Val His
580 585 590

s Trp Gly Glu Lys Ala Glu Gly Gln Trp Thr Leu Glu Ile Gln Asp
595 600 605

u Pro Ser Gln Val Arg Asn Pro Glu Lys Gln Gly Lys Leu Lys Glu
610 615 620

ɔ Ser Leu Ile Leu Tyr Gly Thr Ala Glu His Pro Tyr His Thr Phe
5 630 635 640

r Ala His Gln Ser Arg Ser Arg Met Leu Glu Leu Ser Ala Pro Glu
645 650 655

```
:u Glu Pro Pro Lys Ala Ala Leu Ser Pro Ser Gln Val Glu Val Pro
           660                 665                 670

.u Asp Glu Glu Asp Tyr Thr Ala Gln Ser Thr Pro Gly Ser Ala Asn
       675                 680                 685

.e Leu Gln Thr Ser Val Cys His Pro Glu Cys Gly Asp Lys Gly Cys
   690                 695                 700

:p Gly Pro Asn Ala Asp Gln Cys Leu Asn Cys Val His Phe Ser Leu
'5                 710                 715                 720

.y Ser Val Lys Thr Ser Arg Lys Cys Val Ser Val Cys Pro Leu Gly
               725                 730                 735

'r Phe Gly Asp Thr Ala Ala Arg Arg Cys Arg Arg Cys His Lys Gly
           740                 745                 750

's Glu Thr Cys Ser Ser Arg Ala Ala Thr Gln Cys Leu Ser Cys Arg
       755                 760                 765

g Gly Phe Tyr His His Gln Glu Met Asn Thr Cys Val Thr Leu Cys
  770                 775                 780

o Ala Gly Phe Tyr Ala Asp Glu Ser Gln Lys Asn Cys Leu Lys Cys
5                 790                 795                 800

s Pro Ser Cys Lys Lys Cys Val Asp Glu Pro Glu Lys Cys Thr Val
              805                 810                 815

s Lys Glu Gly Phe Ser Leu Ala Arg Gly Ser Cys Ile Pro Asp Cys
          820                 825                 830

u Pro Gly Thr Tyr Phe Asp Ser Glu Leu Ile Arg Cys Gly Glu Cys
      835                 840                 845

s His Thr Cys Gly Thr Cys Val Gly Pro Gly Arg Glu Glu Cys Ile
  850                 855                 860

s Cys Ala Lys Asn Phe His Phe His Asp Trp Lys Cys Val Pro Ala
5                 870                 875                 880
```

's Gly Glu Gly Phe Tyr Pro Glu Glu Met Pro Gly Leu Pro His Lys
885 890 895

ıl Cys Arg Arg Cys Asp Glu Asn Cys Leu Ser Cys Ala Gly Ser Ser
900 905 910

:g Asn Cys Ser Arg Cys Lys Thr Gly Phe Thr Gln Leu Gly Thr Ser
915 920 925

's Ile Thr Asn His Thr Cys Ser Asn Ala Asp Glu Thr Phe Cys Glu
930 935 940

:t Val Lys Ser Asn Arg Leu Cys Glu Arg Lys Leu Phe Ile Gln Phe
5 950 955 960

's Cys Arg Thr Cys Leu Leu Ala Gly
965

10> 118
11> 683
12> PRT
13> Homo sapiens

00> 118

t Ala Leu Phe Val Arg Leu Leu Ala Leu Ala Leu Ala Leu Ala Leu
5 10 15

y Pro Ala Ala Thr Leu Ala Gly Pro Ala Lys Ser Pro Tyr Gln Leu
20 25 30

l Leu Gln His Ser Arg Leu Arg Gly Arg Gln His Gly Pro Asn Val
35 40 45

s Ala Val Gln Lys Val Ile Gly Thr Asn Arg Lys Tyr Phe Thr Asn
50 55 60

s Lys Gln Trp Tyr Gln Arg Lys Ile Cys Gly Lys Ser Thr Val Ile
70 75 80

r Tyr Glu Cys Cys Pro Gly Tyr Glu Lys Val Pro Gly Glu Lys Gly
85 90 95

eolf-seql-S000001.txt

```
ys Pro Ala Ala Leu Pro Leu Ser Asn Leu Tyr Glu Thr Leu Gly Val
           100                 105                 110

al Gly Ser Thr Thr Thr Gln Leu Tyr Thr Asp Arg Thr Glu Lys Leu
       115                 120                 125

rg Pro Glu Met Glu Gly Pro Gly Ser Phe Thr Ile Phe Ala Pro Ser
   130                 135                 140

sn Glu Ala Trp Ala Ser Leu Pro Ala Glu Val Leu Asp Ser Leu Val
15                 150                 155                 160

er Asn Val Asn Ile Glu Leu Leu Asn Ala Leu Arg Tyr His Met Val
               165                 170                 175

ly Arg Arg Val Leu Thr Asp Glu Leu Lys His Gly Met Thr Leu Thr
           180                 185                 190

er Met Tyr Gln Asn Ser Asn Ile Gln Ile His His Tyr Pro Asn Gly
       195                 200                 205

le Val Thr Val Asn Cys Ala Arg Leu Leu Lys Ala Asp His His Ala
   210                 215                 220

r Asn Gly Val Val His Leu Ile Asp Lys Val Ile Ser Thr Ile Thr
5                  230                 235                 240

n Asn Ile Gln Gln Ile Ile Glu Ile Glu Asp Thr Phe Glu Thr Leu
               245                 250                 255

g Ala Ala Val Ala Ala Ser Gly Leu Asn Thr Met Leu Glu Gly Asn
           260                 265                 270

y Gln Tyr Thr Leu Leu Ala Pro Thr Asn Glu Ala Phe Glu Lys Ile
       275                 280                 285

o Ser Glu Thr Leu Asn Arg Ile Leu Gly Asp Pro Glu Ala Leu Arg
   290                 295                 300

p Leu Leu Asn Asn His Ile Leu Lys Ser Ala Met Cys Ala Glu Ala
5                  310                 315                 320
```

le Val Ala Gly Leu Ser Val Glu Thr Leu Glu Gly Thr Thr Leu Glu
325 330 335

al Gly Cys Ser Gly Asp Met Leu Thr Ile Asn Gly Lys Ala Ile Ile
340 345 350

er Asn Lys Asp Ile Leu Ala Thr Asn Gly Val Ile His Tyr Ile Asp
355 360 365

.u Leu Leu Ile Pro Asp Ser Ala Lys Thr Leu Phe Glu Leu Ala Ala
370 375 380

.u Ser Asp Val Ser Thr Ala Ile Asp Leu Phe Arg Gln Ala Gly Leu
35 390 395 400

.y Asn His Leu Ser Gly Ser Glu Arg Leu Thr Leu Leu Ala Pro Leu
405 410 415

in Ser Val Phe Lys Asp Gly Thr Pro Pro Ile Asp Ala His Thr Arg
420 425 430

in Leu Leu Arg Asn His Ile Ile Lys Asp Gln Leu Ala Ser Lys Tyr
435 440 445

u Tyr His Gly Gln Thr Leu Glu Thr Leu Gly Gly Lys Lys Leu Arg
450 455 460

.l Phe Val Tyr Arg Asn Ser Leu Cys Ile Glu Asn Ser Cys Ile Ala
5 470 475 480

a His Asp Lys Arg Gly Arg Tyr Gly Thr Leu Phe Thr Met Asp Arg
485 490 495

l Leu Thr Pro Pro Met Gly Thr Val Met Asp Val Leu Lys Gly Asp
500 505 510

n Arg Phe Ser Met Leu Val Ala Ala Ile Gln Ser Ala Gly Leu Thr
515 520 525

u Thr Leu Asn Arg Glu Gly Val Tyr Thr Val Phe Ala Pro Thr Asn

```
   530                  535                  540

Lu Ala Phe Arg Ala Leu Pro Pro Arg Glu Arg Ser Arg Leu Leu Gly
15                  550                  555                  560

sp Ala Lys Glu Leu Ala Asn Ile Leu Lys Tyr His Ile Gly Asp Glu
               565                  570                  575

.e Leu Val Ser Gly Gly Ile Gly Ala Leu Val Arg Leu Lys Ser Leu
            580                  585                  590

.n Gly Asp Lys Leu Glu Val Ser Leu Lys Asn Asn Val Val Ser Val
         595                  600                  605

sn Lys Glu Pro Val Ala Glu Pro Asp Ile Met Ala Thr Asn Gly Val
   610                  615                  620

ıl His Val Ile Thr Asn Val Leu Gln Pro Pro Ala Asn Arg Pro Gln
:5                  630                  635                  640

.u Arg Gly Asp Glu Leu Ala Asp Ser Ala Leu Glu Ile Phe Lys Gln
               645                  650                  655

.a Ser Ala Phe Ser Arg Ala Ser Gln Arg Ser Val Arg Leu Ala Pro
            660                  665                  670

.l Tyr Gln Lys Leu Leu Glu Arg Met Lys His
         675                  680


10>  119
11>  381
12>  PRT
13>  Homo sapiens

00>  119

t Glu Ser Gly Ser Thr Ala Ala Ser Glu Glu Ala Arg Ser Leu Arg
               5                   10                   15

u Cys Glu Leu Tyr Val Gln Lys His Asn Ile Gln Ala Leu Leu Lys
            20                   25                   30

p Ser Ile Val Gln Leu Cys Thr Ala Arg Pro Glu Arg Pro Met Ala
```

35 40 45

ıe Leu Arg Glu Tyr Phe Glu Arg Leu Glu Lys Glu Glu Ala Lys Gln
50 55 60

.e Gln Asn Leu Gln Lys Ala Gly Thr Arg Thr Asp Ser Arg Glu Asp
; 70 75 80

.u Ile Ser Pro Pro Pro Pro Asn Pro Val Val Lys Gly Arg Arg Arg
85 90 95

:g Gly Ala Ile Ser Ala Glu Val Tyr Thr Glu Glu Asp Ala Ala Ser
100 105 110

'r Val Arg Lys Val Ile Pro Lys Asp Tyr Lys Thr Met Ala Ala Leu
115 120 125

.a Lys Ala Ile Glu Lys Asn Val Leu Phe Ser His Leu Asp Asp Asn
130 135 140

.u Arg Ser Asp Ile Phe Asp Ala Met Phe Ser Val Ser Phe Ile Ala
5 150 155 160

y Glu Thr Val Ile Gln Gln Gly Asp Glu Gly Asp Asn Phe Tyr Val
165 170 175

e Asp Gln Gly Glu Thr Asp Val Tyr Val Asn Asn Glu Trp Ala Thr
180 185 190

r Val Gly Glu Gly Gly Ser Phe Gly Glu Leu Ala Leu Ile Tyr Gly
195 200 205

r Pro Arg Ala Ala Thr Val Lys Ala Lys Thr Asn Val Lys Leu Trp
210 215 220

y Ile Asp Arg Asp Ser Tyr Arg Arg Ile Leu Met Gly Ser Thr Leu
5 230 235 240

g Lys Arg Lys Met Tyr Glu Glu Phe Leu Ser Lys Val Ser Ile Leu
245 250 255

```
lu Ser Leu Asp Lys Trp Glu Arg Leu Thr Val Ala Asp Ala Leu Glu
            260                     265                     270

:o Val Gln Phe Glu Asp Gly Gln Lys Ile Val Val Gln Gly Glu Pro
        275                     280                     285

ly Asp Glu Phe Phe Ile Ile Leu Glu Gly Ser Ala Ala Val Leu Gln
    290                     295                     300

:g Arg Ser Glu Asn Glu Glu Phe Val Glu Val Gly Arg Leu Gly Pro
)5                      310                     315                     320

er Asp Tyr Phe Gly Glu Ile Ala Leu Leu Met Asn Arg Pro Arg Ala
                325                     330                     335

.a Thr Val Val Ala Arg Gly Pro Leu Lys Cys Val Lys Leu Asp Arg
            340                     345                     350

:o Arg Phe Glu Arg Val Leu Gly Pro Cys Ser Asp Ile Leu Lys Arg
        355                     360                     365

in Ile Gln Gln Tyr Asn Ser Phe Val Ser Leu Ser Val
    370                     375                     380


:10>  120
:11>  245
:12>  PRT
13>  Homo sapiens

00>  120

t Asn Gly Arg Ala Asp Phe Arg Glu Pro Asn Ala Glu Val Pro Arg
                 5                  10                  15

o Ile Pro His Ile Gly Pro Asp Tyr Ile Pro Thr Glu Glu Arg
            20                  25                  30

g Val Phe Ala Glu Cys Asn Asp Glu Ser Phe Trp Phe Arg Ser Val
        35                  40                  45

o Leu Ala Ala Thr Ser Met Leu Ile Thr Gln Gly Leu Ile Ser Lys
    50                  55                  60
```

```
.y Ile Leu Ser Ser His Pro Lys Tyr Gly Ser Ile Pro Lys Leu Ile
5                  70                  75                  80

eu Ala Cys Ile Met Gly Tyr Phe Ala Gly Lys Leu Ser Tyr Val Lys
               85                  90                  95

ır Cys Gln Glu Lys Phe Lys Lys Leu Glu Asn Ser Pro Leu Gly Glu
           100                 105                 110

.a Leu Arg Ser Gly Gln Ala Arg Arg Ser Ser Pro Pro Gly His Tyr
       115                 120                 125

'r Gln Lys Ser Lys Tyr Asp Ser Ser Val Ser Gly Gln Ser Ser Phe
   130                 135                 140

.l Thr Ser Pro Ala Ala Asp Asn Ile Glu Met Leu Pro His Tyr Glu
5                  150                 155                 160

'o Ile Pro Phe Ser Ser Ser Met Asn Glu Ser Ala Pro Thr Gly Ile
               165                 170                 175

.r Asp His Ile Val Gln Gly Pro Asp Pro Asn Leu Glu Glu Ser Pro
           180                 185                 190

s Arg Lys Asn Ile Thr Tyr Glu Glu Leu Arg Asn Lys Asn Arg Glu
       195                 200                 205

r Tyr Glu Val Ser Leu Thr Gln Lys Thr Asp Pro Ser Val Arg Pro
   210                 215                 220

t His Glu Arg Val Pro Lys Lys Glu Val Lys Val Asn Lys Tyr Gly
5                  230                 235                 240

p Thr Trp Asp Glu
               245

10>  121
11>  359
12>  PRT
13>  Homo sapiens

30>  121
```

```
et Ser Thr Arg Ala Lys Lys Leu Arg Arg Ile Trp Arg Ile Leu Glu
               5                   10                  15

lu Glu Glu Ser Val Ala Gly Ala Val Gln Thr Leu Leu Leu Arg Ser
           20                  25                  30

.n Glu Gly Gly Val Thr Ser Ala Ala Ala Ser Thr Leu Ser Glu Pro
       35                  40                  45

:o Arg Arg Thr Gln Glu Ser Arg Thr Arg Thr Arg Ala Leu Gly Leu
   50                  55                  60

:o Thr Leu Pro Met Glu Lys Leu Ala Ala Ser Thr Glu Pro Gln Gly
;                  70                  75                  80

:o Arg Pro Val Leu Gly Arg Glu Ser Val Gln Val Pro Asp Asp Gln
               85                  90                  95

;p Phe Arg Ser Phe Arg Ser Glu Cys Glu Ala Glu Val Gly Trp Asn
           100                 105                 110

:u Thr Tyr Ser Arg Ala Gly Val Ser Val Trp Val Gln Ala Val Glu
       115                 120                 125

:t Asp Arg Thr Leu His Lys Ile Lys Cys Arg Met Glu Cys Cys Asp
   130                 135                 140

.l Pro Ala Glu Thr Leu Tyr Asp Val Leu His Asp Ile Glu Tyr Arg
5                  150                 155                 160

s Lys Trp Asp Ser Asn Val Ile Glu Thr Phe Asp Ile Ala Arg Leu
               165                 170                 175

r Val Asn Ala Asp Val Gly Tyr Tyr Ser Trp Arg Cys Pro Lys Pro
           180                 185                 190

u Lys Asn Arg Asp Val Ile Thr Leu Arg Ser Trp Leu Pro Met Gly
       195                 200                 205

a Asp Tyr Ile Ile Met Asn Tyr Ser Val Lys His Pro Lys Tyr Pro
   210                 215                 220
```

:o Arg Lys Asp Leu Val Arg Ala Val Ser Ile Gln Thr Gly Tyr Leu
:5 230 235 240

.e Gln Ser Thr Gly Pro Lys Ser Cys Val Ile Thr Tyr Leu Ala Gln
245 250 255

ıl Asp Pro Lys Gly Ser Leu Pro Lys Trp Val Val Asn Lys Ser Ser
260 265 270

.n Phe Leu Ala Pro Lys Ala Met Lys Lys Met Tyr Lys Ala Cys Leu
275 280 285

's Tyr Pro Glu Trp Lys Gln Lys His Leu Pro His Phe Lys Pro Trp
290 295 300

:u His Pro Glu Gln Ser Pro Leu Pro Ser Leu Ala Leu Ser Glu Leu
'5 310 315 320

:r Val Gln His Ala Asp Ser Leu Glu Asn Ile Asp Glu Ser Ala Val
325 330 335

a Glu Ser Arg Glu Glu Arg Met Gly Gly Ala Gly Gly Glu Gly Ser
340 345 350

p Asp Asp Thr Ser Leu Thr
355

10> 122
11> 199
12> PRT
13> Homo sapiens

00> 122

t Ser Ser Gly Asn Ala Lys Ile Gly His Pro Ala Pro Asn Phe Lys
5 10 15

a Thr Ala Val Met Pro Asp Gly Gln Phe Lys Asp Ile Ser Leu Ser
20 25 30

ɔ Tyr Lys Gly Lys Tyr Val Val Phe Phe Phe Tyr Pro Leu Asp Phe
35 40 45

ır Phe Val Cys Pro Thr Glu Ile Ile Ala Phe Ser Asp Arg Ala Glu
50 55 60

u Phe Lys Lys Leu Asn Cys Gln Val Ile Gly Ala Ser Val Asp Ser
70 75 80

s Phe Cys His Leu Ala Trp Val Asn Thr Pro Lys Lys Gln Gly Gly
85 90 95

u Gly Pro Met Asn Ile Pro Leu Val Ser Asp Pro Lys Arg Thr Ile
100 105 110

a Gln Asp Tyr Gly Val Leu Lys Ala Asp Glu Gly Ile Ser Phe Arg
115 120 125

y Leu Phe Ile Ile Asp Asp Lys Gly Ile Leu Arg Gln Ile Thr Val
130 135 140

n Asp Leu Pro Val Gly Arg Ser Val Asp Glu Thr Leu Arg Leu Val
5 150 155 160

n Ala Phe Gln Phe Thr Asp Lys His Gly Glu Val Cys Pro Ala Gly
165 170 175

p Lys Pro Gly Ser Asp Thr Ile Lys Pro Asp Val Gln Lys Ser Lys
180 185 190

u Tyr Phe Ser Lys Gln Lys
195

10> 123
11> 219
12> PRT
13> Homo sapiens

)0> 123

: Ser Gly Leu Ser Gly Pro Pro Ala Arg Arg Gly Pro Phe Pro Leu
5 10 15

a Leu Leu Leu Leu Phe Leu Leu Gly Pro Arg Leu Val Leu Ala Ile
20 25 30

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r Phe His Leu Pro Ile Asn Ser Arg Lys Cys Leu Arg Glu Glu Ile
35 40 45

s Lys Asp Leu Leu Val Thr Gly Ala Tyr Glu Ile Ser Asp Gln Ser
50 55 60

y Gly Ala Gly Gly Leu Arg Ser His Leu Arg Ile Thr Asp Ser Ala
70 75 80

y His Ile Leu Tyr Ser Lys Glu Asp Ala Thr Lys Gly Lys Phe Ala
85 90 95

e Thr Thr Glu Asp Tyr Asp Met Phe Glu Val Cys Phe Glu Ser Lys
100 105 110

y Thr Gly Arg Ile Pro Asp Gln Leu Val Ile Leu Asp Met Lys His
115 120 125

y Val Glu Ala Lys Asn Tyr Glu Glu Ile Ala Lys Val Glu Lys Leu
130 135 140

s Pro Leu Glu Val Glu Leu Arg Arg Leu Glu Asp Leu Ser Glu Ser
5 150 155 160

e Val Asn Asp Phe Ala Tyr Met Lys Lys Arg Glu Glu Glu Met Arg
165 170 175

) Thr Asn Glu Ser Thr Asn Thr Arg Val Leu Tyr Phe Ser Ile Phe
180 185 190

: Met Phe Cys Leu Ile Gly Leu Ala Thr Trp Gln Val Phe Tyr Leu
195 200 205

j Arg Phe Phe Lys Ala Lys Lys Leu Ile Glu
210 215

.0> 124
.1> 1575
.2> PRT
.3> Homo sapiens

'0> 124

t Pro His Glu Glu Leu Pro Ser Leu Gln Arg Pro Arg Tyr Gly Ser
5 10 15

e Val Asp Asp Glu Arg Leu Ser Ala Glu Glu Met Asp Glu Arg Arg
20 25 30

g Gln Asn Ile Ala Tyr Glu Tyr Leu Cys His Leu Glu Glu Ala Lys
35 40 45

g Trp Met Glu Val Cys Leu Val Glu Glu Leu Pro Pro Thr Thr Glu
50 55 60

u Glu Glu Gly Leu Arg Asn Gly Val Tyr Leu Ala Lys Leu Ala Lys
70 75 80

e Phe Ala Pro Lys Met Val Ser Glu Lys Lys Ile Tyr Asp Val Glu
85 90 95

n Thr Arg Tyr Lys Lys Ser Gly Leu His Phe Arg His Thr Asp Asn
100 105 110

r Val Gln Trp Leu Arg Ala Met Glu Ser Ile Gly Leu Pro Lys Ile
115 120 125

e Tyr Pro Glu Thr Thr Asp Val Tyr Asp Arg Lys Asn Ile Pro Arg
130 135 140

: Ile Tyr Cys Ile His Ala Leu Ser Leu Tyr Leu Phe Lys Leu Gly
5 150 155 160

e Ala Pro Gln Ile Gln Asp Leu Leu Gly Lys Val Asp Phe Thr Glu
165 170 175

ı Glu Ile Ser Asn Met Arg Lys Glu Leu Glu Lys Tyr Gly Ile Gln
180 185 190

: Pro Ser Phe Ser Lys Ile Gly Gly Ile Leu Ala Asn Glu Leu Ser
195 200 205

. Asp Glu Ala Ala Leu His Ala Ala Val Ile Ala Ile Asn Glu Ala
210 215 220

al Glu Lys Gly Ile Ala Glu Gln Thr Val Val Thr Leu Arg Asn Pro
25 230 235 240

sn Ala Val Leu Thr Leu Val Asp Asp Asn Leu Ala Pro Glu Tyr Gln
245 250 255

ys Glu Leu Trp Asp Ala Lys Lys Lys Lys Glu Glu Asn Ala Arg Leu
260 265 270

ys Asn Ser Cys Ile Ser Glu Glu Glu Arg Asp Ala Tyr Glu Glu Leu
275 280 285

eu Thr Gln Ala Glu Ile Gln Gly Asn Ile Asn Lys Val Asn Arg Gln
290 295 300

la Ala Val Asp His Ile Asn Ala Val Ile Pro Glu Gly Asp Pro Glu
)5 310 315 320

sn Thr Leu Leu Ala Leu Lys Lys Pro Glu Ala Gln Leu Pro Ala Val
325 330 335

yr Pro Phe Ala Ala Ala Met Tyr Gln Asn Glu Leu Phe Asn Leu Gln
340 345 350

ys Gln Asn Thr Met Asn Tyr Leu Ala His Glu Glu Leu Leu Ile Ala
355 360 365

al Glu Met Leu Ser Ala Val Ala Leu Leu Asn Gln Ala Leu Glu Ser
370 375 380

sn Asp Leu Val Ser Val Gln Asn Gln Leu Arg Ser Pro Ala Ile Gly
35 390 395 400

eu Asn Asn Leu Asp Lys Ala Tyr Val Glu Arg Tyr Ala Asn Thr Leu
405 410 415

eu Ser Val Lys Leu Glu Val Leu Ser Gln Gly Gln Asp Asn Leu Ser
420 425 430

p Asn Glu Ile Gln Asn Cys Ile Asp Met Val Asn Ala Gln Ile Gln

435 440 445

lu Glu Asn Asp Arg Val Val Ala Val Gly Tyr Ile Asn Glu Ala Ile
450 455 460

sp Glu Gly Asn Pro Leu Arg Thr Leu Glu Thr Leu Leu Leu Pro Thr
65 470 475 480

la Asn Ile Ser Asp Val Asp Pro Ala His Ala Gln His Tyr Gln Asp
485 490 495

al Leu Tyr His Ala Lys Ser Gln Lys Leu Gly Asp Ser Glu Ser Val
500 505 510

er Lys Val Leu Trp Leu Asp Glu Ile Gln Gln Ala Val Asp Glu Ala
515 520 525

sn Val Asp Glu Asp Arg Ala Lys Gln Trp Val Thr Leu Val Val Asp
530 535 540

al Asn Gln Cys Leu Glu Gly Lys Lys Ser Ser Asp Ile Leu Ser Val
45 550 555 560

eu Lys Ser Ser Thr Ser Asn Ala Asn Asp Ile Ile Pro Glu Cys Ala
565 570 575

sp Lys Tyr Tyr Asp Ala Leu Val Lys Ala Lys Glu Leu Lys Ser Glu
580 585 590

rg Val Ser Ser Asp Gly Ser Trp Leu Lys Leu Asn Leu His Lys Lys
595 600 605

yr Asp Tyr Tyr Tyr Asn Thr Asp Ser Lys Glu Ser Ser Trp Val Thr
610 615 620

ro Glu Ser Cys Phe Tyr Lys Glu Ser Trp Leu Thr Gly Lys Glu Ile
25 630 635 640

u Asp Ile Ile Glu Glu Val Thr Val Gly Tyr Ile Arg Glu Asn Ile
645 650 655

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```
rp Ser Ala Ser Glu Glu Leu Leu Leu Arg Phe Gln Ala Thr Ser Ser
           660                 665                 670

ly Pro Ile Leu Arg Glu Glu Phe Glu Ala Arg Lys Ser Phe Leu His
       675                 680                 685

lu Gln Glu Glu Asn Val Val Lys Ile Gln Ala Phe Trp Lys Gly Tyr
   690                 695                 700

ys Gln Arg Lys Glu Tyr Met His Arg Arg Gln Thr Phe Ile Asp Asn
)5                 710                 715                 720

ır Asp Ser Val Val Lys Ile Gln Ser Trp Phe Arg Met Ala Thr Ala
               725                 730                 735

:g Lys Ser Tyr Leu Ser Arg Leu Gln Tyr Phe Arg Asp His Asn Asn
           740                 745                 750

.u Ile Val Lys Ile Gln Ser Leu Leu Arg Ala Asn Lys Ala Arg Asp
       755                 760                 765

ıp Tyr Lys Thr Leu Val Gly Ser Glu Asn Pro Pro Leu Thr Val Ile
   770                 775                 780

:g Lys Phe Val Tyr Leu Leu Asp Gln Ser Asp Leu Asp Phe Gln Glu
;5                 790                 795                 800

.u Leu Glu Val Ala Arg Leu Arg Glu Glu Val Val Thr Lys Ile Arg
               805                 810                 815

a Asn Gln Gln Leu Glu Lys Asp Leu Asn Leu Met Asp Ile Lys Ile
           820                 825                 830

y Leu Leu Val Lys Asn Arg Ile Thr Leu Glu Asp Val Ile Ser His
       835                 840                 845

r Lys Lys Leu Asn Lys Lys Lys Gly Gly Glu Met Glu Ile Leu Asn
   850                 855                 860

n Thr Asp Asn Gln Gly Ile Lys Ser Leu Ser Lys Glu Arg Arg Lys
5                  870                 875                 880
```

r Leu Glu Thr Tyr Gln Gln Leu Phe Tyr Leu Leu Gln Thr Asn Pro
885 890 895

u Tyr Leu Ala Lys Leu Ile Phe Gln Met Pro Gln Asn Lys Ser Thr
900 905 910

s Phe Met Asp Thr Val Ile Phe Thr Leu Tyr Asn Tyr Ala Ser Asn
915 920 925

n Arg Glu Glu Tyr Leu Leu Leu Lys Leu Phe Lys Thr Ala Leu Glu
930 935 940

u Glu Ile Lys Ser Lys Val Asp Gln Val Gln Asp Ile Val Thr Gly
5 950 955 960

n Pro Thr Val Ile Lys Met Val Val Ser Phe Asn Arg Gly Ala Arg
965 970 975

y Gln Asn Thr Leu Arg Gln Leu Leu Ala Pro Val Val Lys Glu Ile
980 985 990

e Asp Asp Lys Ser Leu Ile Ile Asn Thr Asn Pro Val Glu Val Tyr
995 1000 1005

s Ala Trp Val Asn Gln Leu Glu Thr Gln Thr Gly Glu Ala Ser
1010 1015 1020

s Leu Pro Tyr Asp Val Thr Thr Glu Gln Ala Leu Thr Tyr Pro
1025 1030 1035

a Val Lys Asn Lys Leu Glu Ala Ser Ile Glu Asn Leu Arg Arg
1040 1045 1050

. Thr Asp Lys Val Leu Asn Ser Ile Ile Ser Ser Leu Asp Leu
1055 1060 1065

a Pro Tyr Gly Leu Arg Tyr Ile Ala Lys Val Leu Lys Asn Ser
1070 1075 1080

: His Glu Lys Phe Pro Asp Ala Thr Glu Asp Glu Leu Leu Lys
1085 1090 1095

le Val Gly Asn Leu Leu Tyr Tyr Arg Tyr Met Asn Pro Ala Ile
1100 1105 1110

al Ala Pro Asp Gly Phe Asp Ile Ile Asp Met Thr Ala Gly Gly
1115 1120 1125

ln Ile Asn Ser Asp Gln Arg Arg Asn Leu Gly Ser Val Ala Lys
1130 1135 1140

al Leu Gln His Ala Ala Ser Asn Lys Leu Phe Glu Gly Glu Asn
1145 1150 1155

lu His Leu Ser Ser Met Asn Asn Tyr Leu Ser Glu Thr Tyr Gln
1160 1165 1170

lu Phe Arg Lys Tyr Phe Lys Glu Ala Cys Asn Val Pro Glu Pro
1175 1180 1185

lu Glu Lys Phe Asn Met Asp Lys Tyr Thr Asp Leu Val Thr Val
1190 1195 1200

er Lys Pro Val Ile Tyr Ile Ser Ile Glu Glu Ile Ile Ser Thr
1205 1210 1215

is Ser Leu Leu Leu Glu His Gln Asp Ala Ile Ala Pro Glu Lys
1220 1225 1230

sn Asp Leu Leu Ser Glu Leu Leu Gly Ser Leu Gly Glu Val Pro
1235 1240 1245

ır Val Glu Ser Phe Leu Gly Glu Gly Ala Val Asp Pro Asn Asp
1250 1255 1260

:o Asn Lys Ala Asn Thr Leu Ser Gln Leu Ser Lys Thr Glu Ile
1265 1270 1275

:r Leu Val Leu Thr Ser Lys Tyr Asp Ile Glu Asp Gly Glu Ala
1280 1285 1290

.e Asp Ser Arg Ser Leu Met Ile Lys Thr Lys Lys Leu Ile Ile

1295 1300 1305

sp Val Ile Arg Asn Gln Pro Gly Asn Thr Leu Thr Glu Ile Leu
1310 1315 1320

lu Thr Pro Ala Thr Ala Gln Gln Glu Val Asp His Ala Thr Asp
1325 1330 1335

et Val Ser Arg Ala Met Ile Asp Ser Arg Thr Pro Glu Glu Met
1340 1345 1350

ys His Ser Gln Ser Met Ile Glu Asp Ala Gln Leu Pro Leu Glu
1355 1360 1365

ln Lys Lys Arg Lys Ile Gln Arg Asn Leu Arg Thr Leu Glu Gln
1370 1375 1380

ır Gly His Val Ser Ser Glu Asn Lys Tyr Gln Asp Ile Leu Asn
1385 1390 1395

.u Ile Ala Lys Asp Ile Arg Asn Gln Arg Ile Tyr Arg Lys Leu
1400 1405 1410

:g Lys Ala Glu Leu Ala Lys Leu Gln Gln Thr Leu Asn Ala Leu
1415 1420 1425

ın Lys Lys Ala Ala Phe Tyr Glu Glu Gln Ile Asn Tyr Tyr Asp
1430 1435 1440

ır Tyr Ile Lys Thr Cys Leu Asp Asn Leu Lys Arg Lys Asn Thr
1445 1450 1455

'g Arg Ser Ile Lys Leu Asp Gly Lys Gly Glu Pro Lys Gly Ala
1460 1465 1470

's Arg Ala Lys Pro Val Lys Tyr Thr Ala Ala Lys Leu His Glu
1475 1480 1485

s Gly Val Leu Leu Asp Ile Asp Asp Leu Gln Thr Asn Gln Phe
1490 1495 1500

ys Asn Val Thr Phe Asp Ile Ile Ala Thr Glu Asp Val Gly Ile
1505 1510 1515

he Asp Val Arg Ser Lys Phe Leu Gly Val Glu Met Glu Lys Val
1520 1525 1530

ln Leu Asn Ile Gln Asp Leu Leu Gln Met Gln Tyr Glu Gly Val
1535 1540 1545

la Val Met Lys Met Phe Asp Lys Val Lys Val Asn Val Asn Leu
1550 1555 1560

eu Ile Tyr Leu Leu Asn Lys Lys Phe Tyr Gly Lys
1565 1570 1575

210> 125
211> 212
212> PRT
213> Homo sapiens

400> 125

et Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
5 10 15

al Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
20 25 30

ro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile
35 40 45

hr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly
50 55 60

.n Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala
; 70 75 80

.y Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His
85 90 95

u Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met
100 105 110

al Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu
115 120 125

al Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile
130 135 140

ne Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
45 150 155 160

le Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
165 170 175

sp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
180 185 190

la Thr Asn Ala Thr His Ala Gly Asn Gln Gly Gly Gln Gln Ala Gly
195 200 205

ly Gly Cys Cys
210

210> 126
211> 181
212> PRT
213> Homo sapiens

400> 126

et Gly Asn Ile Phe Ala Asn Leu Phe Lys Gly Leu Phe Gly Lys Lys
5 10 15

u Met Arg Ile Leu Met Val Gly Leu Asp Ala Ala Gly Lys Thr Thr
20 25 30

e Leu Tyr Lys Leu Lys Leu Gly Glu Ile Val Thr Thr Ile Pro Thr
35 40 45

e Gly Phe Asn Val Glu Thr Val Glu Tyr Lys Asn Ile Ser Phe Thr
50 55 60

l Trp Asp Val Gly Gly Gln Asp Lys Ile Arg Pro Leu Trp Arg His
70 75 80

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yr Phe Gln Asn Thr Gln Gly Leu Ile Phe Val Val Asp Ser Asn Asp
85 90 95

rg Glu Arg Val Asn Glu Ala Arg Glu Glu Leu Met Arg Met Leu Ala
100 105 110

lu Asp Glu Leu Arg Asp Ala Val Leu Leu Val Phe Ala Asn Lys Gln
115 120 125

sp Leu Pro Asn Ala Met Asn Ala Ala Glu Ile Thr Asp Lys Leu Gly
130 135 140

eu His Ser Leu Arg His Arg Asn Trp Tyr Ile Gln Ala Thr Cys Ala
45 150 155 160

ar Ser Gly Asp Gly Leu Tyr Glu Gly Leu Asp Trp Leu Ser Asn Gln
165 170 175

eu Arg Asn Gln Lys
180

:10> 127
:11> 732
:12> PRT
:13> Homo sapiens

100> 127

et Pro Glu Glu Thr Gln Thr Gln Asp Gln Pro Met Glu Glu Glu Glu
5 10 15

al Glu Thr Phe Ala Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu
20 25 30

.e Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu
35 40 45

.e Ser Asn Ser Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Thr Leu
50 55 60

.r Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu
70 75 80

le Pro Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Asp Thr Gly Ile
85 90 95

ly Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys
100 105 110

er Gly Thr Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile
115 120 125

er Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val
130 135 140

la Glu Lys Val Thr Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr
45 150 155 160

la Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Thr Asp Thr
165 170 175

ly Glu Pro Met Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu
180 185 190

sp Gln Thr Glu Tyr Leu Glu Glu Arg Arg Ile Lys Glu Ile Val Lys
195 200 205

ys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Phe Val Glu Lys
210 215 220

lu Arg Asp Lys Glu Val Ser Asp Asp Glu Ala Glu Glu Lys Glu Asp
25 230 235 240

ys Glu Glu Glu Lys Glu Lys Glu Glu Lys Glu Ser Glu Asp Lys Pro
245 250 255

.u Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Glu Lys Lys Asp Gly
260 265 270

sp Lys Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu
275 280 285

.u Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile
290 295 300

hr Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp
05 310 315 320

lu Asp His Leu Ala Val Lys His Phe Ser Val Glu Gly Gln Leu Glu
325 330 335

he Arg Ala Leu Leu Phe Val Pro Arg Arg Ala Pro Phe Asp Leu Phe
340 345 350

lu Asn Arg Lys Lys Lys Asn Asn Ile Lys Leu Tyr Val Arg Arg Val
355 360 365

ne Ile Met Asp Asn Cys Glu Glu Leu Ile Pro Glu Tyr Leu Asn Phe
370 375 380

le Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn Ile Ser Arg
35 390 395 400

lu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Leu
405 410 415

al Lys Lys Cys Leu Glu Leu Phe Thr Glu Leu Ala Glu Asp Lys Glu
420 425 430

sn Tyr Lys Lys Phe Tyr Glu Gln Phe Ser Lys Asn Ile Lys Leu Gly
435 440 445

.e His Glu Asp Ser Gln Asn Arg Lys Lys Leu Ser Glu Leu Leu Arg
450 455 460

'r Tyr Thr Ser Ala Ser Gly Asp Glu Met Val Ser Leu Lys Asp Tyr
5 470 475 480

's Thr Arg Met Lys Glu Asn Gln Lys His Ile Tyr Tyr Ile Thr Gly
485 490 495

.u Thr Lys Asp Gln Val Ala Asn Ser Ala Phe Val Glu Arg Leu Arg
500 505 510

's His Gly Leu Glu Val Ile Tyr Met Ile Glu Pro Ile Asp Glu Tyr
515 520 525

```
ys Val Gln Gln Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Ser Val
    530                 535                 540

ır Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Glu Lys Lys Lys
15                  550                 555                 560

ln Glu Glu Lys Lys Thr Lys Phe Glu Asn Leu Cys Lys Ile Met Lys
                565                 570                 575

sp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg Leu
            580                 585                 590

al Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala
        595                 600                 605

sn Met Glu Arg Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr
    610                 615                 620

et Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp His
25                  630                 635                 640

er Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp
                645                 650                 655

's Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu
            660                 665                 670

r Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg Ile
        675                 680                 685

r Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr
    690                 695                 700

a Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu
5                   710                 715                 720

y Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp
                725                 730

10>  128
```

eolf-seql-S000001.txt

211> 858
212> PRT
213> Homo sapiens

400> 128

et Gly Asp His Leu Asp Leu Leu Leu Gly Val Val Leu Met Ala Gly
5 10 15

ro Val Phe Gly Ile Pro Ser Cys Ser Phe Asp Gly Arg Ile Ala Phe
20 25 30

yr Arg Phe Cys Asn Leu Thr Gln Val Pro Gln Val Leu Asn Thr Thr
35 40 45

lu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser
50 55 60

er Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln
5 70 75 80

yr Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn
85 90 95

eu Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro
100 105 110

sp Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu Tyr Phe
115 120 125

ys Gly Leu Ser Asp Ala Val Leu Lys Asp Gly Tyr Phe Arg Asn Leu
130 135 140

ys Ala Leu Thr Arg Leu Asp Leu Ser Lys Asn Gln Ile Arg Ser Leu
15 150 155 160

r Leu His Pro Ser Phe Gly Lys Leu Asn Ser Leu Lys Ser Ile Asp
165 170 175

ie Ser Ser Asn Gln Ile Phe Leu Val Cys Glu His Glu Leu Glu Pro
180 185 190

u Gln Gly Lys Thr Leu Ser Phe Phe Ser Leu Ala Ala Asn Ser Leu

195 200 205

yr Ser Arg Val Ser Val Asp Trp Gly Lys Cys Met Asn Pro Phe Arg
210 215 220

sn Met Val Leu Glu Ile Leu Asp Val Ser Gly Asn Gly Trp Thr Val
25 230 235 240

sp Ile Thr Gly Asn Phe Ser Asn Ala Ile Ser Lys Ser Gln Ala Phe
245 250 255

er Leu Ile Leu Ala His His Ile Met Gly Ala Gly Phe Gly Phe His
260 265 270

sn Ile Lys Asp Pro Asp Gln Asn Thr Phe Ala Gly Leu Ala Arg Ser
275 280 285

er Val Arg His Leu Asp Leu Ser His Gly Phe Val Phe Ser Leu Asn
290 295 300

er Arg Val Phe Glu Thr Leu Lys Asp Leu Lys Val Leu Asn Leu Ala
)5 310 315 320

yr Asn Lys Ile Asn Lys Ile Ala Asp Glu Ala Phe Tyr Gly Leu Asp
325 330 335

sn Leu Gln Val Leu Asn Leu Ser Tyr Asn Leu Leu Gly Glu Leu Tyr
340 345 350

er Ser Asn Phe Tyr Gly Leu Pro Lys Val Ala Tyr Ile Asp Leu Gln
355 360 365

's Asn His Ile Ala Ile Ile Gln Asp Gln Thr Phe Lys Phe Leu Glu
370 375 380

's Leu Gln Thr Leu Asp Leu Arg Asp Asn Ala Leu Thr Thr Ile His
35 390 395 400

ie Ile Pro Ser Ile Pro Asp Ile Phe Leu Ser Gly Asn Lys Leu Val
405 410 415

hr Leu Pro Lys Ile Asn Leu Thr Ala Asn Leu Ile His Leu Ser Glu
420 425 430

sn Arg Leu Glu Asn Leu Asp Ile Leu Tyr Phe Leu Leu Arg Val Pro
435 440 445

is Leu Gln Ile Leu Ile Leu Asn Gln Asn Arg Phe Ser Ser Cys Ser
450 455 460

ly Asp Gln Thr Pro Ser Glu Asn Pro Ser Leu Glu Gln Leu Phe Leu
55 470 475 480

ly Glu Asn Met Leu Gln Leu Ala Trp Glu Thr Glu Leu Cys Trp Asp
485 490 495

al Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu Asn His Asn
500 505 510

/r Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu Thr Ala Leu
515 520 525

:g Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu Ser His Asn
530 535 540

sp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg Asn Gln Leu
15 550 555 560

eu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val Leu Asp Ile
565 570 575

ır His Asn Lys Phe Ile Cys Glu Cys Glu Leu Ser Thr Phe Ile Asn
580 585 590

:p Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro Ala Asp Ile
595 600 605

'r Cys Val Tyr Pro Asp Ser Phe Ser Gly Val Ser Leu Phe Ser Leu
610 615 620

r Thr Glu Gly Cys Asp Glu Glu Glu Val Leu Lys Ser Leu Lys Phe
5 630 635 640

er Leu Phe Ile Val Cys Thr Val Thr Leu Thr Leu Phe Leu Met Thr
645 650 655

le Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile Cys Tyr Lys
660 665 670

hr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly Thr Glu Pro
675 680 685

sp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser Lys Asp Phe
690 695 700

ır Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln Tyr Ser
)5 710 715 720

sp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe Val Pro
725 730 735

ly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn Ser Arg
740 745 750

ys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly Trp Cys
755 760 765

eu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp Leu Asn
770 775 780

er Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr Gln Leu
35 790 795 800

et Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln Tyr Leu
805 810 815

rg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His Lys Leu
820 825 830

er Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp Asn Asn
835 840 845

e Pro Leu Gln Thr Val Ala Thr Ile Ser
850 855

210> 129
211> 466
212> PRT
213> Homo sapiens

400> 129

et Val Met Glu Lys Pro Ser Pro Leu Leu Val Gly Arg Glu Phe Val
5 10 15

rg Gln Tyr Tyr Thr Leu Leu Asn Gln Ala Pro Asp Met Leu His Arg
20 25 30

ne Tyr Gly Lys Asn Ser Ser Tyr Val His Gly Gly Leu Asp Ser Asn
35 40 45

Ly Lys Pro Ala Asp Ala Val Tyr Gly Gln Lys Glu Ile His Arg Lys
50 55 60

al Met Ser Gln Asn Phe Thr Asn Cys His Thr Lys Ile Arg His Val
5 70 75 80

sp Ala His Ala Thr Leu Asn Asp Gly Val Val Val Gln Val Met Gly
85 90 95

eu Leu Ser Asn Asn Asn Gln Ala Leu Arg Arg Phe Met Gln Thr Phe
100 105 110

l Leu Ala Pro Glu Gly Ser Val Ala Asn Lys Phe Tyr Val His Asn
115 120 125

p Ile Phe Arg Tyr Gln Asp Glu Val Phe Gly Gly Phe Val Thr Glu
130 135 140

o Gln Glu Glu Ser Glu Glu Glu Val Glu Glu Pro Glu Glu Arg Gln
5 150 155 160

n Thr Pro Glu Val Val Pro Asp Asp Ser Gly Thr Phe Tyr Asp Gln
165 170 175

a Val Val Ser Asn Asp Met Glu Glu His Leu Glu Glu Pro Val Ala
180 185 190

lu Pro Glu Pro Asp Pro Glu Pro Glu Pro Glu Gln Glu Pro Val Ser
195 200 205

lu Ile Gln Glu Glu Lys Pro Glu Pro Val Leu Glu Glu Thr Ala Pro
210 215 220

lu Asp Ala Gln Lys Ser Ser Ser Pro Ala Pro Ala Asp Ile Ala Gln
25 230 235 240

hr Val Gln Glu Asp Leu Arg Thr Phe Ser Trp Ala Ser Val Thr Ser
245 250 255

ys Asn Leu Pro Pro Ser Gly Ala Val Pro Val Thr Gly Ile Pro Pro
260 265 270

is Val Val Lys Val Pro Ala Ser Gln Pro Arg Pro Glu Ser Lys Pro
275 280 285

lu Ser Gln Ile Pro Pro Gln Arg Pro Gln Arg Asp Gln Arg Val Arg
290 295 300

lu Gln Arg Ile Asn Ile Pro Pro Gln Arg Gly Pro Arg Pro Ile Arg
)5 310 315 320

lu Ala Gly Glu Gln Gly Asp Ile Glu Pro Arg Arg Met Val Arg His
325 330 335

:o Asp Ser His Gln Leu Phe Ile Gly Asn Leu Pro His Glu Val Asp
340 345 350

's Ser Glu Leu Lys Asp Phe Phe Gln Ser Tyr Gly Asn Val Val Glu
355 360 365

:u Arg Ile Asn Ser Gly Gly Lys Leu Pro Asn Phe Gly Phe Val Val
370 375 380

ie Asp Asp Ser Glu Pro Val Gln Lys Val Leu Ser Asn Arg Pro Ile
:5 390 395 400

t Phe Arg Gly Glu Val Arg Leu Asn Val Glu Glu Lys Lys Thr Arg

405 410 415

la Ala Arg Glu Gly Asp Arg Arg Asp Asn Arg Leu Arg Gly Pro Gly
420 425 430

ly Pro Arg Gly Gly Leu Gly Gly Gly Met Arg Gly Pro Pro Arg Gly
435 440 445

ly Met Val Gln Lys Pro Gly Phe Gly Val Gly Arg Gly Leu Ala Pro
450 455 460

:g Gln
55

<210> 130
<211> 245
<212> PRT
<213> Homo sapiens

<400> 130

et Thr Leu Phe Pro Val Leu Leu Phe Leu Val Ala Gly Leu Leu Pro
5 10 15

er Phe Pro Ala Asn Glu Asp Lys Asp Pro Ala Phe Thr Ala Leu Leu
20 25 30

ır Thr Gln Thr Gln Val Gln Arg Glu Ile Val Asn Lys His Asn Glu
35 40 45

:u Arg Arg Ala Val Ser Pro Pro Ala Arg Asn Met Leu Lys Met Glu
50 55 60

'p Asn Lys Glu Ala Ala Ala Asn Ala Gln Lys Trp Ala Asn Gln Cys
70 75 80

n Tyr Arg His Ser Asn Pro Lys Asp Arg Met Thr Ser Leu Lys Cys
85 90 95

y Glu Asn Leu Tyr Met Ser Ser Ala Ser Ser Ser Trp Ser Gln Ala
100 105 110

e Gln Ser Trp Phe Asp Glu Tyr Asn Asp Phe Asp Phe Gly Val Gly

115 120 125

ro Lys Thr Pro Asn Ala Val Val Gly His Tyr Thr Gln Val Val Trp
130 135 140

yr Ser Ser Tyr Leu Val Gly Cys Gly Asn Ala Tyr Cys Pro Asn Gln
45 150 155 160

ys Val Leu Lys Tyr Tyr Tyr Val Cys Gln Tyr Cys Pro Ala Gly Asn
165 170 175

rp Ala Asn Arg Leu Tyr Val Pro Tyr Glu Gln Gly Ala Pro Cys Ala
180 185 190

er Cys Pro Asp Asn Cys Asp Asp Gly Leu Cys Thr Asn Gly Cys Lys
195 200 205

yr Glu Asp Leu Tyr Ser Asn Cys Lys Ser Leu Lys Leu Thr Leu Thr
210 215 220

ys Lys His Gln Leu Val Arg Asp Ser Cys Lys Ala Ser Cys Asn Cys
25 230 235 240

er Asn Ser Ile Tyr
245

10> 131
11> 202
12> PRT
13> Homo sapiens

00> 131

t Cys Thr Gly Gly Cys Ala Arg Cys Leu Gly Gly Thr Leu Ile Pro
5 10 15

u Ala Phe Phe Gly Phe Leu Ala Asn Ile Leu Leu Phe Phe Pro Gly
20 25 30

y Lys Val Ile Asp Asp Asn Asp His Leu Ser Gln Glu Ile Trp Phe
35 40 45

e Gly Gly Ile Leu Gly Ser Gly Val Leu Met Ile Phe Pro Ala Leu

50 55 60

al Phe Leu Gly Leu Lys Asn Asn Asp Cys Cys Gly Cys Cys Gly Asn
5 70 75 80

lu Gly Cys Gly Lys Arg Phe Ala Met Phe Thr Ser Thr Ile Phe Ala
85 90 95

al Val Gly Phe Leu Gly Ala Gly Tyr Ser Phe Ile Ile Ser Ala Ile
100 105 110

er Ile Asn Lys Gly Pro Lys Cys Leu Met Ala Asn Ser Thr Trp Gly
115 120 125

yr Pro Phe His Asp Gly Asp Tyr Leu Asn Asp Glu Ala Leu Trp Asn
130 135 140

ys Cys Arg Glu Pro Leu Asn Val Val Pro Trp Asn Leu Thr Leu Phe
45 150 155 160

er Ile Leu Leu Val Val Gly Gly Ile Gln Met Val Leu Cys Ala Ile
165 170 175

n Val Val Asn Gly Leu Leu Gly Thr Leu Cys Gly Asp Cys Gln Cys
180 185 190

s Gly Cys Cys Gly Gly Asp Gly Pro Val
195 200

10> 132
11> 295
12> PRT
13> Homo sapiens

00> 132

t Gln Pro Glu Gly Ala Glu Lys Gly Lys Ser Phe Lys Gln Arg Leu
5 10 15

l Leu Lys Ser Ser Leu Ala Lys Glu Thr Leu Ser Glu Phe Leu Gly
20 25 30

r Phe Ile Leu Ile Val Leu Gly Cys Gly Cys Val Ala Gln Ala Ile

35 40 45

eu Ser Arg Gly Arg Phe Gly Gly Val Ile Thr Ile Asn Val Gly Phe
50 55 60

er Met Ala Val Ala Met Ala Ile Tyr Val Ala Gly Gly Val Ser Gly
5 70 75 80

ly His Ile Asn Pro Ala Val Ser Leu Ala Met Cys Leu Phe Gly Arg
85 90 95

et Lys Trp Phe Lys Leu Pro Phe Tyr Val Gly Ala Gln Phe Leu Gly
100 105 110

la Phe Val Gly Ala Ala Thr Val Phe Gly Ile Tyr Tyr Asp Gly Leu
115 120 125

et Ser Phe Ala Gly Gly Lys Leu Leu Ile Val Gly Glu Asn Ala Thr
130 135 140

la His Ile Phe Ala Thr Tyr Pro Ala Pro Tyr Leu Ser Leu Ala Asn
45 150 155 160

la Phe Ala Asp Gln Val Val Ala Thr Met Ile Leu Leu Ile Ile Val
165 170 175

ne Ala Ile Phe Asp Ser Arg Asn Leu Gly Ala Pro Arg Gly Leu Glu
180 185 190

ro Ile Ala Ile Gly Leu Leu Ile Ile Val Ile Ala Ser Ser Leu Gly
195 200 205

eu Asn Ser Gly Cys Ala Met Asn Pro Ala Arg Asp Leu Ser Pro Arg
210 215 220

eu Phe Thr Ala Leu Ala Gly Trp Gly Phe Glu Val Phe Arg Ala Gly
25 230 235 240

sn Asn Phe Trp Trp Ile Pro Val Val Gly Pro Leu Val Gly Ala Val
245 250 255

```
le Gly Gly Leu Ile Tyr Val Leu Val Ile Glu Ile His His Pro Glu
           260                 265                 270

ro Asp Ser Val Phe Lys Ala Glu Gln Ser Glu Asp Lys Pro Glu Lys
       275                 280                 285

yr Glu Leu Ser Val Ile Met
   290                 295


210>  133
211>  288
212>  PRT
213>  Homo sapiens

400>  133

et Trp Leu Pro Ala Leu Val Leu Ala Thr Leu Ala Ala Ser Ala Ala
               5                   10                  15

rp Ala Val His Pro Ser Ser Pro Pro Val Val Asp Thr Val His Gly
           20                  25                  30

ys Val Leu Gly Lys Phe Ile Ser Leu Glu Gly Phe Ala Gln Pro Val
       35                  40                  45

la Val Phe Leu Gly Ile Pro Phe Ala Lys Pro Pro Leu Gly Pro Leu
   50                  55                  60

rg Phe Thr Pro Pro Gln Pro Ala Glu Pro Trp Ser Phe Val Lys Asn
5                  70                  75                  80

a Thr Leu Tyr Pro Pro Met Phe Thr Gln Asp Pro Arg Arg Gly Gly
               85                  90                  95

n Leu Ile Ser Glu Leu Phe Thr Asn Arg Lys Glu Asn Ile Pro Leu
           100                 105                 110

s Leu Ser Glu Asp Cys Leu Tyr Leu Asn Ile Tyr Thr Pro Ala Asp
       115                 120                 125

u Thr Lys Lys Asn Arg Leu Pro Val Met Val Trp Ile His Gly Gly
   130                 135                 140
```

```
ly Leu Met Val Gly Ala Ala Ser Thr Tyr Asp Gly Leu Ala Leu Ala
45                 150                 155                 160

la His Glu Asn Val Val Val Val Thr Ile Gln Tyr Arg Leu Gly Ile
               165                 170                 175

rp Gly Phe Phe Ser Thr Gly Asp Glu His Ser Pro Gly Asn Trp Gly
           180                 185                 190

is Leu Asp Gln Leu Ala Ala Leu His Trp Val Gln Asp Asn Ile Ala
       195                 200                 205

er Phe Gly Gly Asn Pro Gly Ser Val Thr Ile Phe Gly Gly Ser Ala
   210                 215                 220

ly Gly Glu Ser Val Ser Val Leu Val Leu Ser Pro Leu Ala Lys Asn
25                 230                 235                 240

eu Phe His Arg Ala Ile Ser Glu Ser Gly Val Ala Leu Thr Ser Val
               245                 250                 255

eu Val Lys Lys Gly Asp Val Lys Pro Leu Ala Glu Val Gly Leu Arg
           260                 265                 270

eu Val Arg Leu Trp Leu Asp Thr His Thr Ser Leu Ala Leu Cys Ser
       275                 280                 285

10>  134
11>  98
12>  PRT
13>  Homo sapiens

00>  134

t Met Cys Gly Ala Pro Ser Ala Thr Gln Pro Ala Thr Ala Glu Thr
               5                   10                  15

n His Ile Ala Asp Gln Val Arg Ser Gln Leu Glu Glu Lys Glu Asn
           20                  25                  30

s Lys Phe Pro Val Phe Lys Ala Val Ser Phe Lys Ser Gln Val Val
       35                  40                  45
```

eolf-seql-S000001.txt

la Gly Thr Asn Tyr Phe Ile Lys Val His Val Gly Asp Glu Asp Phe
50 55 60

al His Leu Arg Val Phe Gln Ser Leu Pro His Glu Asn Lys Pro Leu
5 70 75 80

hr Leu Ser Asn Tyr Gln Thr Asn Lys Ala Lys His Asp Glu Leu Thr
85 90 95

yr Phe

210> 135
211> 254
212> PRT
213> Homo sapiens

400> 135

et Ala Ser Leu Leu Lys Val Asp Gln Glu Val Lys Leu Lys Val Asp
5 10 15

er Phe Arg Glu Arg Ile Thr Ser Glu Ala Glu Asp Leu Val Ala Asn
20 25 30

he Phe Pro Lys Lys Leu Leu Glu Leu Asp Ser Phe Leu Lys Glu Pro
35 40 45

le Leu Asn Ile His Asp Leu Thr Gln Ile His Ser Asp Met Asn Leu
50 55 60

ro Val Pro Asp Pro Ile Leu Leu Thr Asn Ser His Asp Gly Leu Asp
5 70 75 80

y Pro Thr Tyr Lys Lys Arg Arg Leu Asp Glu Cys Glu Glu Ala Phe
85 90 95

n Gly Thr Lys Val Phe Val Met Pro Asn Gly Met Leu Lys Ser Asn
100 105 110

n Gln Leu Val Asp Ile Ile Glu Lys Val Lys Pro Glu Ile Arg Leu
115 120 125

```
eu Ile Glu Lys Cys Asn Thr Val Lys Met Trp Val Gln Leu Leu Ile
   130                 135                 140

ro Arg Ile Glu Asp Gly Asn Asn Phe Gly Val Ser Ile Gln Glu Glu
45                 150                 155                 160

hr Val Ala Glu Leu Arg Thr Val Glu Ser Glu Ala Ala Ser Tyr Leu
               165                 170                 175

sp Gln Ile Ser Arg Tyr Tyr Ile Thr Arg Ala Lys Leu Val Ser Lys
           180                 185                 190

le Ala Lys Tyr Pro His Val Glu Asp Tyr Arg Arg Thr Val Thr Glu
       195                 200                 205

le Asp Glu Lys Glu Tyr Ile Ser Leu Arg Leu Ile Ile Ser Glu Leu
   210                 215                 220

rg Asn Gln Tyr Val Thr Leu His Asp Met Ile Leu Lys Asn Ile Glu
25                 230                 235                 240

ys Ile Lys Arg Pro Arg Ser Ser Asn Ala Glu Thr Leu Tyr
               245                 250


210>  136
211>  189
212>  PRT
213>  Homo sapiens

400>  136

et Gly Leu Gly Ala Arg Gly Ala Trp Ala Ala Leu Leu Leu Gly Thr
               5                   10                  15

eu Gln Val Leu Ala Leu Leu Gly Ala Ala His Glu Ser Ala Ala Met
           20                  25                  30

.a Glu Thr Leu Gln His Val Pro Ser Asp His Thr Asn Glu Thr Ser
       35                  40                  45

n Ser Thr Val Lys Pro Pro Thr Ser Val Ala Ser Asp Ser Ser Asn
   50                  55                  60
```

hr Thr Val Thr Thr Met Lys Pro Thr Ala Ala Ser Asn Thr Thr Thr
5 70 75 80

ro Gly Met Val Ser Thr Asn Met Thr Ser Thr Thr Leu Lys Ser Thr
85 90 95

ro Lys Thr Thr Ser Val Ser Gln Asn Thr Ser Gln Ile Ser Thr Ser
100 105 110

ır Met Thr Val Thr His Asn Ser Ser Val Thr Ser Ala Ala Ser Ser
115 120 125

al Thr Ile Thr Thr Thr Met His Ser Glu Ala Lys Lys Gly Ser Lys
130 135 140

ıe Asp Thr Gly Ser Phe Val Gly Gly Ile Val Leu Thr Leu Gly Val
15 150 155 160

eu Ser Ile Leu Tyr Ile Gly Cys Lys Met Tyr Tyr Ser Arg Arg Gly
165 170 175

le Arg Tyr Arg Thr Ile Asp Glu His Asp Ala Ile Ile
180 185

:10> 137
:11> 2314
:12> PRT
:13> Homo sapiens

100> 137

et Arg Ile Leu Lys Arg Phe Leu Ala Cys Ile Gln Leu Leu Cys Val
5 10 15

's Arg Leu Asp Trp Ala Asn Gly Tyr Tyr Arg Gln Gln Arg Lys Leu
20 25 30

.l Glu Glu Ile Gly Trp Ser Tyr Thr Gly Ala Leu Asn Gln Lys Asn
35 40 45

p Gly Lys Lys Tyr Pro Thr Cys Asn Ser Pro Lys Gln Ser Pro Ile
50 55 60

sn Ile Asp Glu Asp Leu Thr Gln Val Asn Val Asn Leu Lys Lys Leu
5 70 75 80

ys Phe Gln Gly Trp Asp Lys Thr Ser Leu Glu Asn Thr Phe Ile His
85 90 95

sn Thr Gly Lys Thr Val Glu Ile Asn Leu Thr Asn Asp Tyr Arg Val
100 105 110

er Gly Gly Val Ser Glu Met Val Phe Lys Ala Ser Lys Ile Thr Phe
115 120 125

is Trp Gly Lys Cys Asn Met Ser Ser Asp Gly Ser Glu His Ser Leu
130 135 140

lu Gly Gln Lys Phe Pro Leu Glu Met Gln Ile Tyr Cys Phe Asp Ala
45 150 155 160

sp Arg Phe Ser Ser Phe Glu Glu Ala Val Lys Gly Lys Gly Lys Leu
165 170 175

rg Ala Leu Ser Ile Leu Phe Glu Val Gly Thr Glu Glu Asn Leu Asp
180 185 190

ne Lys Ala Ile Ile Asp Gly Val Glu Ser Val Ser Arg Phe Gly Lys
195 200 205

ln Ala Ala Leu Asp Pro Phe Ile Leu Leu Asn Leu Leu Pro Asn Ser
210 215 220

ır Asp Lys Tyr Tyr Ile Tyr Asn Gly Ser Leu Thr Ser Pro Pro Cys
25 230 235 240

ır Asp Thr Val Asp Trp Ile Val Phe Lys Asp Thr Val Ser Ile Ser
245 250 255

.u Ser Gln Leu Ala Val Phe Cys Glu Val Leu Thr Met Gln Gln Ser
260 265 270

.y Tyr Val Met Leu Met Asp Tyr Leu Gln Asn Asn Phe Arg Glu Gln
275 280 285

ln Tyr Lys Phe Ser Arg Gln Val Phe Ser Ser Tyr Thr Gly Lys Glu
290 295 300

lu Ile His Glu Ala Val Cys Ser Ser Glu Pro Glu Asn Val Gln Ala
05 310 315 320

sp Pro Glu Asn Tyr Thr Ser Leu Leu Val Thr Trp Glu Arg Pro Arg
325 330 335

al Val Tyr Asp Thr Met Ile Glu Lys Phe Ala Val Leu Tyr Gln Gln
340 345 350

eu Asp Gly Glu Asp Gln Thr Lys His Glu Phe Leu Thr Asp Gly Tyr
355 360 365

ln Asp Leu Gly Ala Ile Leu Asn Asn Leu Leu Pro Asn Met Ser Tyr
370 375 380

al Leu Gln Ile Val Ala Ile Cys Thr Asn Gly Leu Tyr Gly Lys Tyr
85 390 395 400

er Asp Gln Leu Ile Val Asp Met Pro Thr Asp Asn Pro Glu Leu Asp
405 410 415

eu Phe Pro Glu Leu Ile Gly Thr Glu Glu Ile Ile Lys Glu Glu Glu
420 425 430

lu Gly Lys Asp Ile Glu Glu Gly Ala Ile Val Asn Pro Gly Arg Asp
435 440 445

er Ala Thr Asn Gln Ile Arg Lys Lys Glu Pro Gln Ile Ser Thr Thr
450 455 460

hr His Tyr Asn Arg Ile Gly Thr Lys Tyr Asn Glu Ala Lys Thr Asn
65 470 475 480

rg Ser Pro Thr Arg Gly Ser Glu Phe Ser Gly Lys Gly Asp Val Pro
485 490 495

sn Thr Ser Leu Asn Ser Thr Ser Gln Pro Val Thr Lys Leu Ala Thr
500 505 510

lu Lys Asp Ile Ser Leu Thr Ser Gln Thr Val Thr Glu Leu Pro Pro
515 520 525

is Thr Val Glu Gly Thr Ser Ala Ser Leu Asn Asp Gly Ser Lys Thr
530 535 540

al Leu Arg Ser Pro His Met Asn Leu Ser Gly Thr Ala Glu Ser Leu
45 550 555 560

sn Thr Val Ser Ile Thr Glu Tyr Glu Glu Glu Ser Leu Leu Thr Ser
565 570 575

he Lys Leu Asp Thr Gly Ala Glu Asp Ser Ser Gly Ser Ser Pro Ala
580 585 590

hr Ser Ala Ile Pro Phe Ile Ser Glu Asn Ile Ser Gln Gly Tyr Ile
595 600 605

he Ser Ser Glu Asn Pro Glu Thr Ile Thr Tyr Asp Val Leu Ile Pro
610 615 620

lu Ser Ala Arg Asn Ala Ser Glu Asp Ser Thr Ser Ser Gly Ser Glu
25 630 635 640

lu Ser Leu Lys Asp Pro Ser Met Glu Gly Asn Val Trp Phe Pro Ser
645 650 655

er Thr Asp Ile Thr Ala Gln Pro Asp Val Gly Ser Gly Arg Glu Ser
660 665 670

he Leu Gln Thr Asn Tyr Thr Glu Ile Arg Val Asp Glu Ser Glu Lys
675 680 685

hr Thr Lys Ser Phe Ser Ala Gly Pro Val Met Ser Gln Gly Pro Ser
690 695 700

al Thr Asp Leu Glu Met Pro His Tyr Ser Thr Phe Ala Tyr Phe Pro
05 710 715 720

hr Glu Val Thr Pro His Ala Phe Thr Pro Ser Ser Arg Gln Gln Asp

```
               725                 730                 735

eu Val Ser Thr Val Asn Val Val Tyr Ser Gln Thr Thr Gln Pro Val
           740                 745                 750

yr Asn Gly Glu Thr Pro Leu Gln Pro Ser Tyr Ser Ser Glu Val Phe
       755                 760                 765

ro Leu Val Thr Pro Leu Leu Leu Asp Asn Gln Ile Leu Asn Thr Thr
   770                 775                 780

ro Ala Ala Ser Ser Ser Asp Ser Ala Leu His Ala Thr Pro Val Phe
85                 790                 795                 800

ro Ser Val Asp Val Ser Phe Glu Ser Ile Leu Ser Ser Tyr Asp Gly
               805                 810                 815

la Pro Leu Leu Pro Phe Ser Ser Ala Ser Phe Ser Ser Glu Leu Phe
           820                 825                 830

rg His Leu His Thr Val Ser Gln Ile Leu Pro Gln Val Thr Ser Ala
       835                 840                 845

nr Glu Ser Asp Lys Val Pro Leu His Ala Ser Leu Pro Val Ala Gly
   850                 855                 860

ly Asp Leu Leu Leu Glu Pro Ser Leu Ala Gln Tyr Ser Asp Val Leu
55                 870                 875                 880

er Thr Thr His Ala Ala Ser Glu Thr Leu Glu Phe Gly Ser Glu Ser
               885                 890                 895

ly Val Leu Tyr Lys Thr Leu Met Phe Ser Gln Val Glu Pro Pro Ser
           900                 905                 910

er Asp Ala Met Met His Ala Arg Ser Ser Gly Pro Glu Pro Ser Tyr
       915                 920                 925

a Leu Ser Asp Asn Glu Gly Ser Gln His Ile Phe Thr Val Ser Tyr
   930                 935                 940
```

er Ser Ala Ile Pro Val His Asp Ser Val Gly Val Thr Tyr Gln Gly
45 950 955 960

er Leu Phe Ser Gly Pro Ser His Ile Pro Ile Pro Lys Ser Ser Leu
965 970 975

le Thr Pro Thr Ala Ser Leu Leu Gln Pro Thr His Ala Leu Ser Gly
980 985 990

sp Gly Glu Trp Ser Gly Ala Ser Ser Asp Ser Glu Phe Leu Leu Pro
995 1000 1005

sp Thr Asp Gly Leu Thr Ala Leu Asn Ile Ser Ser Pro Val Ser
1010 1015 1020

al Ala Glu Phe Thr Tyr Thr Thr Ser Val Phe Gly Asp Asp Asn
1025 1030 1035

ys Ala Leu Ser Lys Ser Glu Ile Ile Tyr Gly Asn Glu Thr Glu
1040 1045 1050

eu Gln Ile Pro Ser Phe Asn Glu Met Val Tyr Pro Ser Glu Ser
1055 1060 1065

ır Val Met Pro Asn Met Tyr Asp Asn Val Asn Lys Leu Asn Ala
1070 1075 1080

er Leu Gln Glu Thr Ser Val Ser Ile Ser Ser Thr Lys Gly Met
1085 1090 1095

ıe Pro Gly Ser Leu Ala His Thr Thr Thr Lys Val Phe Asp His
1100 1105 1110

.u Ile Ser Gln Val Pro Glu Asn Asn Phe Ser Val Gln Pro Thr
1115 1120 1125

.s Thr Val Ser Gln Ala Ser Gly Asp Thr Ser Leu Lys Pro Val
1130 1135 1140

ːu Ser Ala Asn Ser Glu Pro Ala Ser Ser Asp Pro Ala Ser Ser
1145 1150 1155

lu Met Leu Ser Pro Ser Thr Gln Leu Leu Phe Tyr Glu Thr Ser
1160 1165 1170

la Ser Phe Ser Thr Glu Val Leu Leu Gln Pro Ser Phe Gln Ala
1175 1180 1185

er Asp Val Asp Thr Leu Leu Lys Thr Val Leu Pro Ala Val Pro
1190 1195 1200

er Asp Pro Ile Leu Val Glu Thr Pro Lys Val Asp Lys Ile Ser
1205 1210 1215

er Thr Met Leu His Leu Ile Val Ser Asn Ser Ala Ser Ser Glu
1220 1225 1230

sn Met Leu His Ser Thr Ser Val Pro Val Phe Asp Val Ser Pro
1235 1240 1245

nr Ser His Met His Ser Ala Ser Leu Gln Gly Leu Thr Ile Ser
1250 1255 1260

yr Ala Ser Glu Lys Tyr Glu Pro Val Leu Leu Lys Ser Glu Ser
1265 1270 1275

er His Gln Val Val Pro Ser Leu Tyr Ser Asn Asp Glu Leu Phe
1280 1285 1290

ln Thr Ala Asn Leu Glu Ile Asn Gln Ala His Pro Pro Lys Gly
1295 1300 1305

rg His Val Phe Ala Thr Pro Val Leu Ser Ile Asp Glu Pro Leu
1310 1315 1320

sn Thr Leu Ile Asn Lys Leu Ile His Ser Asp Glu Ile Leu Thr
1325 1330 1335

er Thr Lys Ser Ser Val Thr Gly Lys Val Phe Ala Gly Ile Pro
1340 1345 1350

ir Val Ala Ser Asp Thr Phe Val Ser Thr Asp His Ser Val Pro
1355 1360 1365

le Gly Asn Gly His Val Ala Ile Thr Ala Val Ser Pro His Arg
1370 1375 1380

sp Gly Ser Val Thr Ser Thr Lys Leu Leu Phe Pro Ser Lys Ala
1385 1390 1395

hr Ser Glu Leu Ser His Ser Ala Lys Ser Asp Ala Gly Leu Val
1400 1405 1410

ly Gly Gly Glu Asp Gly Asp Thr Asp Asp Asp Gly Asp Asp Asp
1415 1420 1425

sp Asp Arg Asp Ser Asp Gly Leu Ser Ile His Lys Cys Met Ser
1430 1435 1440

ys Ser Ser Tyr Arg Glu Ser Gln Glu Lys Val Met Asn Asp Ser
1445 1450 1455

sp Thr His Glu Asn Ser Leu Met Asp Gln Asn Asn Pro Ile Ser
1460 1465 1470

yr Ser Leu Ser Glu Asn Ser Glu Glu Asp Asn Arg Val Thr Ser
1475 1480 1485

al Ser Ser Asp Ser Gln Thr Gly Met Asp Arg Ser Pro Gly Lys
1490 1495 1500

er Pro Ser Ala Asn Gly Leu Ser Gln Lys His Asn Asp Gly Lys
1505 1510 1515

u Glu Asn Asp Ile Gln Thr Gly Ser Ala Leu Leu Pro Leu Ser
1520 1525 1530

o Glu Ser Lys Ala Trp Ala Val Leu Thr Ser Asp Glu Glu Ser
1535 1540 1545

y Ser Gly Gln Gly Thr Ser Asp Ser Leu Asn Glu Asn Glu Thr
1550 1555 1560

r Thr Asp Phe Ser Phe Ala Asp Thr Asn Glu Lys Asp Ala Asp

1565 1570 1575

ly Ile Leu Ala Ala Gly Asp Ser Glu Ile Thr Pro Gly Phe Pro
1580 1585 1590

ln Ser Pro Thr Ser Ser Val Thr Ser Glu Asn Ser Glu Val Phe
1595 1600 1605

is Val Ser Glu Ala Glu Ala Ser Asn Ser Ser His Glu Ser Arg
1610 1615 1620

le Gly Leu Ala Glu Gly Leu Glu Ser Glu Lys Lys Ala Val Ile
1625 1630 1635

ro Leu Val Ile Val Ser Ala Leu Thr Phe Ile Cys Leu Val Val
1640 1645 1650

eu Val Gly Ile Leu Ile Tyr Trp Arg Lys Cys Phe Gln Thr Ala
1655 1660 1665

is Phe Tyr Leu Glu Asp Ser Thr Ser Pro Arg Val Ile Ser Thr
1670 1675 1680

ro Pro Thr Pro Ile Phe Pro Ile Ser Asp Asp Val Gly Ala Ile
1685 1690 1695

ro Ile Lys His Phe Pro Lys His Val Ala Asp Leu His Ala Ser
1700 1705 1710

er Gly Phe Thr Glu Glu Phe Glu Thr Leu Lys Glu Phe Tyr Gln
1715 1720 1725

u Val Gln Ser Cys Thr Val Asp Leu Gly Ile Thr Ala Asp Ser
1730 1735 1740

r Asn His Pro Asp Asn Lys His Lys Asn Arg Tyr Ile Asn Ile
1745 1750 1755

l Ala Tyr Asp His Ser Arg Val Lys Leu Ala Gln Leu Ala Glu
1760 1765 1770

ys Asp Gly Lys Leu Thr Asp Tyr Ile Asn Ala Asn Tyr Val Asp
1775 1780 1785

ly Tyr Asn Arg Pro Lys Ala Tyr Ile Ala Ala Gln Gly Pro Leu
1790 1795 1800

ys Ser Thr Ala Glu Asp Phe Trp Arg Met Ile Trp Glu His Asn
1805 1810 1815

al Glu Val Ile Val Met Ile Thr Asn Leu Val Glu Lys Gly Arg
1820 1825 1830

rg Lys Cys Asp Gln Tyr Trp Pro Ala Asp Gly Ser Glu Glu Tyr
1835 1840 1845

ly Asn Phe Leu Val Thr Gln Lys Ser Val Gln Val Leu Ala Tyr
1850 1855 1860

yr Thr Val Arg Asn Phe Thr Leu Arg Asn Thr Lys Ile Lys Lys
1865 1870 1875

ly Ser Gln Lys Gly Arg Pro Ser Gly Arg Val Val Thr Gln Tyr
1880 1885 1890

is Tyr Thr Gln Trp Pro Asp Met Gly Val Pro Glu Tyr Ser Leu
1895 1900 1905

ro Val Leu Thr Phe Val Arg Lys Ala Ala Tyr Ala Lys Arg His
1910 1915 1920

a Val Gly Pro Val Val Val His Cys Ser Ala Gly Val Gly Arg
1925 1930 1935

ır Gly Thr Tyr Ile Val Leu Asp Ser Met Leu Gln Gln Ile Gln
1940 1945 1950

s Glu Gly Thr Val Asn Ile Phe Gly Phe Leu Lys His Ile Arg
1955 1960 1965

r Gln Arg Asn Tyr Leu Val Gln Thr Glu Glu Gln Tyr Val Phe
1970 1975 1980

le His Asp Thr Leu Val Glu Ala Ile Leu Ser Lys Glu Thr Glu
1985 1990 1995

al Leu Asp Ser His Ile His Ala Tyr Val Asn Ala Leu Leu Ile
2000 2005 2010

ro Gly Pro Ala Gly Lys Thr Lys Leu Glu Lys Gln Phe Gln Leu
2015 2020 2025

eu Ser Gln Ser Asn Ile Gln Gln Ser Asp Tyr Ser Ala Ala Leu
2030 2035 2040

ys Gln Cys Asn Arg Glu Lys Asn Arg Thr Ser Ser Ile Ile Pro
2045 2050 2055

al Glu Arg Ser Arg Val Gly Ile Ser Ser Leu Ser Gly Glu Gly
2060 2065 2070

ır Asp Tyr Ile Asn Ala Ser Tyr Ile Met Gly Tyr Tyr Gln Ser
2075 2080 2085

sn Glu Phe Ile Ile Thr Gln His Pro Leu Leu His Thr Ile Lys
2090 2095 2100

sp Phe Trp Arg Met Ile Trp Asp His Asn Ala Gln Leu Val Val
2105 2110 2115

et Ile Pro Asp Gly Gln Asn Met Ala Glu Asp Glu Phe Val Tyr
2120 2125 2130

rp Pro Asn Lys Asp Glu Pro Ile Asn Cys Glu Ser Phe Lys Val
2135 2140 2145

ır Leu Met Ala Glu Glu His Lys Cys Leu Ser Asn Glu Glu Lys
2150 2155 2160

u Ile Ile Gln Asp Phe Ile Leu Glu Ala Thr Gln Asp Asp Tyr
2165 2170 2175

l Leu Glu Val Arg His Phe Gln Cys Pro Lys Trp Pro Asn Pro
2180 2185 2190

sp Ser Pro Ile Ser Lys Thr Phe Glu Leu Ile Ser Val Ile Lys
2195 2200 2205

lu Glu Ala Ala Asn Arg Asp Gly Pro Met Ile Val His Asp Glu
2210 2215 2220

is Gly Gly Val Thr Ala Gly Thr Phe Cys Ala Leu Thr Thr Leu
2225 2230 2235

et His Gln Leu Glu Lys Glu Asn Ser Val Asp Val Tyr Gln Val
2240 2245 2250

la Lys Met Ile Asn Leu Met Arg Pro Gly Val Phe Ala Asp Ile
2255 2260 2265

lu Gln Tyr Gln Phe Leu Tyr Lys Val Ile Leu Ser Leu Val Ser
2270 2275 2280

hr Arg Gln Glu Glu Asn Pro Ser Thr Ser Leu Asp Ser Asn Gly
2285 2290 2295

la Ala Leu Pro Asp Gly Asn Ile Ala Glu Ser Leu Glu Ser Leu
2300 2305 2310

al

210> 138
211> 372
212> PRT
213> Homo sapiens

100> 138

et Lys Gln Leu Pro Val Leu Glu Pro Gly Asp Lys Pro Arg Lys Ala
5 10 15

ır Trp Tyr Thr Leu Thr Val Pro Gly Asp Ser Pro Cys Ala Arg Val
20 25 30

.y His Ser Cys Ser Tyr Leu Pro Pro Val Gly Asn Ala Lys Arg Gly
35 40 45

```
ys Val Phe Ile Val Gly Gly Ala Asn Pro Asn Arg Ser Phe Ser Asp
    50                  55                  60

al His Thr Met Asp Leu Gly Lys His Gln Trp Asp Leu Asp Thr Cys
5                   70                  75                  80

ys Gly Leu Leu Pro Arg Tyr Glu His Ala Ser Phe Ile Pro Ser Cys
                85                  90                  95

hr Pro Asp Arg Ile Trp Val Phe Gly Gly Ala Asn Gln Ser Gly Asn
            100                 105                 110

rg Asn Cys Leu Gln Val Leu Asn Pro Glu Thr Arg Thr Trp Thr Thr
        115                 120                 125

ro Glu Val Thr Ser Pro Pro Pro Ser Pro Arg Thr Phe His Thr Ser
    130                 135                 140

er Ala Ala Ile Gly Asn Gln Leu Tyr Val Phe Gly Gly Gly Glu Arg
15                  150                 155                 160

ly Ala Gln Pro Val Gln Asp Thr Lys Leu His Val Phe Asp Ala Asn
                165                 170                 175

hr Leu Thr Trp Ser Gln Pro Glu Thr Leu Gly Asn Pro Pro Ser Pro
            180                 185                 190

rg His Gly His Val Met Val Ala Ala Gly Thr Lys Leu Phe Ile His
        195                 200                 205

y Gly Leu Ala Gly Asp Arg Phe Tyr Asp Asp Leu His Cys Ile Asp
    210                 215                 220

e Ser Asp Met Lys Trp Gln Lys Leu Asn Pro Thr Gly Ala Ala Pro
5                   230                 235                 240

a Gly Cys Ala Ala His Ser Ala Val Ala Met Gly Lys His Val Tyr
                245                 250                 255

e Phe Gly Gly Met Thr Pro Ala Gly Ala Leu Asp Thr Met Tyr Gln
```

260 265 270

yr His Thr Glu Glu Gln His Trp Thr Leu Leu Lys Phe Asp Thr Leu
275 280 285

eu Pro Pro Gly Arg Leu Asp His Ser Met Cys Ile Ile Pro Trp Pro
290 295 300

al Thr Cys Ala Ser Glu Lys Glu Asp Ser Asn Ser Leu Thr Leu Asn
05 310 315 320

is Glu Ala Glu Lys Glu Asp Ser Ala Asp Lys Val Met Ser His Ser
325 330 335

ly Asp Ser His Glu Glu Ser Gln Thr Ala Thr Leu Leu Cys Leu Val
340 345 350

he Gly Gly Met Asn Thr Glu Gly Glu Ile Tyr Asp Asp Cys Ile Val
355 360 365

hr Val Val Asp
370

210> 139
211> 425
212> PRT
213> Homo sapiens

400> 139

et Ala Asp Lys Glu Ala Ala Phe Asp Asp Ala Val Glu Glu Arg Val
5 10 15

le Asn Glu Glu Tyr Lys Ile Trp Lys Lys Asn Thr Pro Phe Leu Tyr
20 25 30

sp Leu Val Met Thr His Ala Leu Glu Trp Pro Ser Leu Thr Ala Gln
35 40 45

rp Leu Pro Asp Val Thr Arg Pro Glu Gly Lys Asp Phe Ser Ile His
50 55 60

rg Leu Val Leu Gly Thr His Thr Ser Asp Glu Gln Asn His Leu Val

5 70 75 80

le Ala Ser Val Gln Leu Pro Asn Asp Asp Ala Gln Phe Asp Ala Ser
85 90 95

is Tyr Asp Ser Glu Lys Gly Glu Phe Gly Gly Phe Gly Ser Val Ser
100 105 110

ly Lys Ile Glu Ile Glu Ile Lys Ile Asn His Glu Gly Glu Val Asn
115 120 125

rg Ala Arg Tyr Met Pro Gln Asn Pro Cys Ile Ile Ala Thr Lys Thr
130 135 140

ro Ser Ser Asp Val Leu Val Phe Asp Tyr Thr Lys His Pro Ser Lys
45 150 155 160

ro Asp Pro Ser Gly Glu Cys Asn Pro Asp Leu Arg Leu Arg Gly His
165 170 175

ln Lys Glu Gly Tyr Gly Leu Ser Trp Asn Pro Asn Leu Ser Gly His
180 185 190

eu Leu Ser Ala Ser Asp Asp His Thr Ile Cys Leu Trp Asp Ile Ser
195 200 205

la Val Pro Lys Glu Gly Lys Val Val Asp Ala Lys Thr Ile Phe Thr
210 215 220

y His Thr Ala Val Val Glu Asp Val Ser Trp His Leu Leu His Glu
25 230 235 240

er Leu Phe Gly Ser Val Ala Asp Asp Gln Lys Leu Met Ile Trp Asp
245 250 255

r Arg Ser Asn Asn Thr Ser Lys Pro Ser His Ser Val Asp Ala His
260 265 270

r Ala Glu Val Asn Cys Leu Ser Phe Asn Pro Tyr Ser Glu Phe Ile
275 280 285

```
eu Ala Thr Gly Ser Ala Asp Lys Thr Val Ala Leu Trp Asp Leu Arg
   290                 295                 300

sn Leu Lys Leu Lys Leu His Ser Phe Glu Ser His Lys Asp Glu Ile
05                 310                 315                 320

he Gln Val Gln Trp Ser Pro His Asn Glu Thr Ile Leu Ala Ser Ser
               325                 330                 335

ly Thr Asp Arg Arg Leu Asn Val Trp Asp Leu Ser Lys Ile Gly Glu
            340                 345                 350

lu Gln Ser Pro Glu Asp Ala Glu Asp Gly Pro Pro Glu Leu Leu Phe
        355                 360                 365

le His Gly Gly His Thr Ala Lys Ile Ser Asp Phe Ser Trp Asn Pro
   370                 375                 380

sn Glu Pro Trp Val Ile Cys Ser Val Ser Glu Asp Asn Ile Met Gln
85                 390                 395                 400

al Trp Gln Met Ala Glu Asn Ile Tyr Asn Asp Glu Asp Pro Glu Gly
               405                 410                 415

er Val Asp Pro Glu Gly Gln Gly Ser
            420                 425


210>  140
211>  633
212>  PRT
213>  Homo sapiens

400>  140

et Asn Pro Ser Ala Pro Ser Tyr Pro Met Ala Ser Leu Tyr Val Gly
               5                   10                  15

sp Leu His Pro Asp Val Thr Glu Ala Met Leu Tyr Glu Lys Phe Ser
            20                  25                  30

ro Ala Gly Pro Ile Leu Ser Ile Arg Val Cys Arg Asp Met Ile Thr
        35                  40                  45
```

```
rg Arg Ser Leu Gly Tyr Ala Tyr Val Asn Phe Gln Gln Pro Ala Asp
   50                  55                  60

la Glu Arg Ala Leu Asp Thr Met Asn Phe Asp Val Ile Lys Gly Lys
5                  70                  75                  80

ro Val Arg Ile Met Trp Ser Gln Arg Asp Pro Ser Leu Arg Lys Ser
               85                  90                  95

ly Val Gly Asn Ile Phe Ile Lys Asn Leu Asp Lys Ser Ile Asp Asn
           100                 105                 110

ys Ala Leu Tyr Asp Thr Phe Ser Ala Phe Gly Asn Ile Leu Ser Cys
       115                 120                 125

ys Val Val Cys Asp Glu Asn Gly Ser Lys Gly Tyr Gly Phe Val His
   130                 135                 140

ne Glu Thr Gln Glu Ala Ala Glu Arg Ala Ile Glu Lys Met Asn Gly
45                 150                 155                 160

et Leu Leu Asn Asp Arg Lys Val Phe Val Gly Arg Phe Lys Ser Arg
               165                 170                 175

ys Glu Arg Glu Ala Glu Leu Gly Ala Arg Ala Lys Glu Phe Thr Asn
           180                 185                 190

al Tyr Ile Lys Asn Phe Gly Glu Asp Met Asp Asp Glu Arg Leu Lys
       195                 200                 205

sp Leu Phe Gly Pro Ala Leu Ser Val Lys Val Met Thr Asp Glu Ser
   210                 215                 220

.y Lys Ser Lys Gly Phe Gly Phe Val Ser Phe Glu Arg His Glu Asp
25                 230                 235                 240

.a Gln Lys Ala Val Asp Glu Met Asn Gly Lys Glu Leu Asn Gly Lys
               245                 250                 255

.n Ile Tyr Val Gly Arg Ala Gln Lys Lys Val Glu Arg Gln Thr Glu
           260                 265                 270
```

eu Lys Arg Lys Phe Glu Gln Met Lys Gln Asp Arg Ile Thr Arg Tyr
275 280 285

ln Gly Val Asn Leu Tyr Val Lys Asn Leu Asp Asp Gly Ile Asp Asp
290 295 300

lu Arg Leu Arg Lys Glu Phe Ser Pro Phe Gly Thr Ile Thr Ser Ala
05 310 315 320

ys Val Met Met Glu Gly Gly Arg Ser Lys Gly Phe Gly Phe Val Cys
325 330 335

he Ser Ser Pro Glu Glu Ala Thr Lys Ala Val Thr Glu Met Asn Gly
340 345 350

rg Ile Val Ala Thr Lys Pro Leu Tyr Val Ala Leu Ala Gln Arg Lys
355 360 365

lu Glu Arg Gln Ala His Leu Thr Asn Gln Tyr Met Gln Arg Met Ala
370 375 380

er Val Arg Ala Val Pro Asn Pro Val Ile Asn Pro Tyr Gln Pro Ala
35 390 395 400

ro Pro Ser Gly Tyr Phe Met Ala Ala Ile Pro Gln Thr Gln Asn Arg
405 410 415

la Ala Tyr Tyr Pro Pro Ser Gln Val Ala Gln Leu Arg Pro Ser Pro
420 425 430

rg Trp Thr Ala Gln Gly Ala Arg Pro His Pro Phe Gln Asn Met Pro
435 440 445

.y Ala Ile Arg Pro Ala Ala Pro Arg Pro Pro Phe Ser Thr Met Arg
450 455 460

ro Ala Ser Ser Gln Val Pro Arg Val Met Ser Thr Gln Arg Val Ala
65 470 475 480

n Thr Ser Thr Gln Thr Met Gly Pro Arg Pro Ala Ala Ala Ala Ala
485 490 495

la Ala Thr Pro Ala Val Arg Thr Val Pro Gln Tyr Lys Tyr Ala Ala
500 505 510

ly Val Arg Asn Pro Gln Gln His Leu Asn Ala Gln Pro Gln Val Thr
515 520 525

et Gln Gln Pro Ala Val His Val Gln Gly Gln Glu Pro Leu Thr Ala
530 535 540

er Met Leu Ala Ser Ala Pro Pro Gln Glu Gln Lys Gln Met Leu Gly
45 550 555 560

lu Arg Leu Phe Pro Leu Ile Gln Ala Met His Pro Thr Leu Ala Gly
565 570 575

ys Ile Thr Gly Met Leu Leu Glu Ile Asp Asn Ser Glu Leu Leu His
580 585 590

et Leu Glu Ser Pro Glu Ser Leu Arg Ser Lys Val Asp Glu Ala Val
595 600 605

la Val Leu Gln Ala His Gln Ala Lys Glu Ala Ala Gln Lys Ala Val
610 615 620

sn Ser Ala Thr Gly Val Pro Thr Val
25 630

:10> 141
:11> 420
:12> PRT
:13> Homo sapiens

100> 141

:t Met Tyr Ser Pro Ile Cys Leu Thr Gln Asp Glu Phe His Pro Phe
5 10 15

:t Glu Ala Leu Leu Pro His Val Arg Ala Ile Ala Tyr Thr Trp Phe
20 25 30

.n Leu Gln Ala Arg Lys Arg Lys Tyr Phe Lys Lys His Glu Lys Arg
35 40 45

eolf-seql-S000001.txt

et Ser Lys Asp Glu Glu Arg Ala Val Lys Asp Glu Leu Leu Ser Glu
50 55 60

ys Pro Glu Ile Lys Gln Lys Trp Ala Ser Arg Leu Leu Ala Lys Leu
5 70 75 80

rg Lys Asp Ile Arg Gln Glu Tyr Arg Glu Asp Phe Val Leu Thr Val
85 90 95

hr Gly Lys Lys His Pro Cys Cys Val Leu Ser Asn Pro Asp Gln Lys
100 105 110

ly Lys Ile Arg Arg Ile Asp Cys Leu Arg Gln Ala Asp Lys Val Trp
115 120 125

rg Leu Asp Leu Val Met Val Ile Leu Phe Lys Gly Ile Pro Leu Glu
130 135 140

er Thr Asp Gly Glu Arg Leu Met Lys Ser Pro His Cys Thr Asn Pro
45 150 155 160

la Leu Cys Val Gln Pro His His Ile Thr Val Ser Val Lys Glu Leu
165 170 175

sp Leu Phe Leu Ala Tyr Tyr Val Gln Glu Gln Asp Ser Gly Gln Ser
180 185 190

y Ser Pro Ser His Asn Asp Pro Ala Lys Asn Pro Pro Gly Tyr Leu
195 200 205

u Asp Ser Phe Val Lys Ser Gly Val Phe Asn Val Ser Glu Leu Val
210 215 220

g Val Ser Arg Thr Pro Ile Thr Gln Gly Thr Gly Val Asn Phe Pro
5 230 235 240

e Gly Glu Ile Pro Ser Gln Pro Tyr Tyr His Asp Met Asn Ser Gly
245 250 255

l Asn Leu Gln Arg Ser Leu Ser Ser Pro Pro Ser Ser Lys Arg Pro

260 265 270

ys Thr Ile Ser Ile Asp Glu Asn Met Glu Pro Ser Pro Thr Gly Asp
275 280 285

he Tyr Pro Ser Pro Ser Ser Pro Ala Ala Gly Ser Arg Thr Trp His
290 295 300

lu Arg Asp Gln Asp Met Ser Ser Pro Thr Thr Met Lys Lys Pro Glu
)5 310 315 320

ys Pro Leu Phe Ser Ser Ala Ser Pro Gln Asp Ser Ser Pro Arg Leu
325 330 335

er Thr Phe Pro Gln His His His Pro Gly Ile Pro Gly Val Ala His
340 345 350

er Val Ile Ser Thr Arg Thr Pro Pro Pro Pro Ser Pro Leu Pro Phe
355 360 365

ro Thr Gln Ala Ile Leu Pro Pro Ala Pro Ser Ser Tyr Phe Ser His
370 375 380

ro Thr Ile Arg Tyr Pro Pro His Leu Asn Pro Gln Asp Thr Leu Lys
35 390 395 400

sn Tyr Val Pro Ser Tyr Asp Pro Ser Ser Pro Gln Thr Ser Gln Ser
405 410 415

rp Tyr Leu Gly
420

:10> 142
:11> 248
:12> PRT
:13> Homo sapiens

00> 142

t Glu Gly Val Glu Glu Lys Lys Lys Glu Val Pro Ala Val Pro Glu
5 . 10 15

r Leu Lys Lys Lys Arg Arg Asn Phe Ala Glu Leu Lys Ile Lys Arg

20 25 30

eu Arg Lys Lys Phe Ala Gln Lys Met Leu Arg Lys Ala Arg Arg Lys
35 40 45

eu Ile Tyr Glu Lys Ala Lys His Tyr His Lys Glu Tyr Arg Gln Met
50 55 60

yr Arg Thr Glu Ile Arg Met Ala Arg Met Ala Arg Lys Ala Gly Asn
5 70 75 80

he Tyr Val Pro Ala Glu Pro Lys Leu Ala Phe Val Ile Arg Ile Arg
85 90 95

ly Ile Asn Gly Val Ser Pro Lys Val Arg Lys Val Leu Gln Leu Leu
100 105 110

rg Leu Arg Gln Ile Phe Asn Gly Thr Phe Val Lys Leu Asn Lys Ala
115 120 125

er Ile Asn Met Leu Arg Ile Val Glu Pro Tyr Ile Ala Trp Gly Tyr
130 135 140

ro Asn Leu Lys Ser Val Asn Glu Leu Ile Tyr Lys Arg Gly Tyr Gly
45 150 155 160

ys Ile Asn Lys Lys Arg Ile Ala Leu Thr Asp Asn Ala Leu Ile Ala
165 170 175

rg Ser Leu Gly Lys Tyr Gly Ile Ile Cys Met Glu Asp Leu Ile His
180 185 190

.u Ile Tyr Thr Val Gly Lys Arg Phe Lys Glu Ala Asn Asn Phe Leu
195 200 205

rp Pro Phe Lys Leu Ser Ser Pro Arg Gly Gly Met Lys Lys Lys Thr
210 215 220

ır His Phe Val Glu Gly Gly Asp Ala Gly Asn Arg Glu Asp Gln Ile
:5 230 235 240

eolf-seql-S000001.txt

sn Arg Leu Ile Arg Arg Met Asn
245

210> 143
211> 420
212> PRT
213> Homo sapiens

400> 143

et Glu Val Pro Pro Arg Leu Ser His Val Pro Pro Pro Leu Phe Pro
5 10 15

er Ala Pro Ala Thr Leu Ala Ser Arg Ser Leu Ser His Trp Arg Pro
20 25 30

rg Pro Pro Arg Gln Leu Ala Pro Leu Leu Pro Ser Leu Ala Pro Ser
35 40 45

er Ala Arg Gln Gly Ala Arg Arg Ala Gln Arg His Val Thr Ala Gln
50 55 60

ln Pro Ser Arg Leu Ala Gly Gly Ala Ala Ile Lys Gly Gly Arg Arg
5 70 75 80

rg Arg Pro Asp Leu Phe Arg Arg His Phe Lys Ser Ser Ser Ile Gln
85 90 95

rg Ser Ala Ala Ala Ala Ala Ala Thr Arg Thr Ala Arg Gln His Pro
100 105 110

ro Ala Asp Ser Ser Val Thr Met Glu Asp Met Asn Glu Tyr Ser Asn
115 120 125

le Glu Glu Phe Ala Glu Gly Ser Lys Ile Asn Ala Ser Lys Asn Gln
130 135 140

n Asp Asp Gly Lys Met Phe Ile Gly Gly Leu Ser Trp Asp Thr Ser
5 150 155 160

s Lys Asp Leu Thr Glu Tyr Leu Ser Arg Phe Gly Glu Val Val Asp
165 170 175

eolf-seql-S000001.txt

ys Thr Ile Lys Thr Asp Pro Val Thr Gly Arg Ser Arg Gly Phe Gly
180 185 190

he Val Leu Phe Lys Asp Ala Ala Ser Val Asp Lys Val Leu Glu Leu
195 200 205

ys Glu His Lys Leu Asp Gly Lys Leu Ile Asp Pro Lys Arg Ala Lys
210 215 220

la Leu Lys Gly Lys Glu Pro Pro Lys Lys Val Phe Val Gly Gly Leu
25 230 235 240

er Pro Asp Thr Ser Glu Glu Gln Ile Lys Glu Tyr Phe Gly Ala Phe
245 250 255

ly Glu Ile Glu Asn Ile Glu Leu Pro Met Asp Thr Lys Thr Asn Glu
260 265 270

rg Arg Gly Phe Cys Phe Ile Thr Tyr Thr Asp Glu Glu Pro Val Lys
275 280 285

ys Leu Leu Glu Ser Arg Tyr His Gln Ile Gly Ser Gly Lys Cys Glu
290 295 300

le Lys Val Ala Gln Pro Lys Glu Val Tyr Arg Gln Gln Gln Gln Gln
05 310 315 320

n Lys Gly Gly Arg Gly Ala Ala Ala Gly Gly Arg Gly Gly Thr Arg
325 330 335

y Arg Gly Arg Gly Gln Gly Gln Asn Trp Asn Gln Gly Phe Asn Asn
340 345 350

r Tyr Asp Gln Gly Tyr Gly Asn Tyr Asn Ser Ala Tyr Gly Gly Asp
355 360 365

n Asn Tyr Ser Gly Tyr Gly Gly Tyr Asp Tyr Thr Gly Tyr Asn Tyr
370 375 380

y Asn Tyr Gly Tyr Gly Gln Gly Tyr Ala Asp Tyr Ser Gly Gln Gln
5 390 395 400

```
er Thr Tyr Gly Lys Ala Ser Arg Gly Gly Gly Asn His Gln Asn Asn
               405                 410                 415

yr Gln Pro Tyr
           420


210>  144
211>  46
212>  PRT
213>  Homo sapiens

400>  144

et Leu Leu Ser Arg Gly Val Leu Pro Phe Leu Ser Tyr Met Lys Phe
               5                   10                  15

eu Ser Gln Glu Arg Gln Asp Tyr Ile Phe Phe Phe Phe Phe Ser Ser
           20                  25                  30

eu Ser Trp Cys Ser Val Phe Leu Val Ile Arg Ile Leu Ile
       35                  40                  45


210>  145
211>  76
212>  PRT
213>  Homo sapiens

400>  145

et Ser Lys Ala His Pro Pro Glu Leu Lys Lys Phe Met Asp Lys Lys
               5                   10                  15

eu Ser Leu Lys Leu Asn Gly Gly Arg His Val Gln Gly Ile Leu Arg
           20                  25                  30

y Phe Asp Pro Phe Met Asn Leu Val Ile Asp Glu Cys Val Glu Met
       35                  40                  45

a Thr Ser Gly Gln Gln Asn Asn Ile Gly Met Val Val Ile Arg Gly
   50                  55                  60

n Ser Ile Ile Met Leu Glu Ala Leu Glu Arg Val
                   70                  75
```

eolf-seql-S000001.txt

210> 146
211> 184
212> PRT
213> Homo sapiens

400> 146

et Arg Glu Tyr Lys Leu Val Val Leu Gly Ser Gly Gly Val Gly Lys
5 10 15

er Ala Leu Thr Val Gln Phe Val Gln Gly Ile Phe Val Glu Lys Tyr
20 25 30

sp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Glu Val Asp Cys
35 40 45

ln Gln Cys Met Leu Glu Ile Leu Asp Thr Ala Gly Thr Glu Gln Phe
50 55 60

hr Ala Met Arg Asp Leu Tyr Met Lys Asn Gly Gln Gly Phe Ala Leu
5 70 75 80

al Tyr Ser Ile Thr Ala Gln Ser Thr Phe Asn Asp Leu Gln Asp Leu
85 90 95

rg Glu Gln Ile Leu Arg Val Lys Asp Thr Glu Asp Val Pro Met Ile
100 105 110

eu Val Gly Asn Lys Cys Asp Leu Glu Asp Glu Arg Val Val Gly Lys
115 120 125

lu Gln Gly Gln Asn Leu Ala Arg Gln Trp Cys Asn Cys Ala Phe Leu
130 135 140

lu Ser Ser Ala Lys Ser Lys Ile Asn Val Asn Glu Ile Phe Tyr Asp
15 150 155 160

eu Val Arg Gln Ile Asn Arg Lys Thr Pro Val Glu Lys Lys Lys Pro
165 170 175

's Lys Lys Ser Cys Leu Leu Leu
180

eolf-seql-S000001.txt

210> 147
211> 440
212> PRT
213> Homo sapiens

400> 147

et Glu Gln Arg Gly Gln Asn Ala Pro Ala Ala Ser Gly Ala Arg Lys
5 10 15

rg His Gly Pro Gly Pro Arg Glu Ala Arg Gly Ala Arg Pro Gly Leu
20 25 30

rg Val Pro Lys Thr Leu Val Leu Val Val Ala Ala Val Leu Leu Leu
35 40 45

al Ser Ala Glu Ser Ala Leu Ile Thr Gln Gln Asp Leu Ala Pro Gln
50 55 60

ln Arg Ala Ala Pro Gln Gln Lys Arg Ser Ser Pro Ser Glu Gly Leu
5 70 75 80

ys Pro Pro Gly His His Ile Ser Glu Asp Gly Arg Asp Cys Ile Ser
85 90 95

ys Lys Tyr Gly Gln Asp Tyr Ser Thr His Trp Asn Asp Leu Leu Phe
100 105 110

ys Leu Arg Cys Thr Arg Cys Asp Ser Gly Glu Val Glu Leu Ser Pro
115 120 125

s Thr Thr Thr Arg Asn Thr Val Cys Gln Cys Glu Glu Gly Thr Phe
130 135 140

g Glu Glu Asp Ser Pro Glu Met Cys Arg Lys Cys Arg Thr Gly Cys
5 150 155 160

o Arg Gly Met Val Lys Val Gly Asp Cys Thr Pro Trp Ser Asp Ile
165 170 175

u Cys Val His Lys Glu Ser Gly Thr Lys His Ser Gly Glu Ala Pro
180 185 190

```
la Val Glu Glu Thr Val Thr Ser Ser Pro Gly Thr Pro Ala Ser Pro
       195                 200                 205

ys Ser Leu Ser Gly Ile Ile Ile Gly Val Thr Val Ala Ala Val Val
   210                 215                 220

eu Ile Val Ala Val Phe Val Cys Lys Ser Leu Leu Trp Lys Lys Val
25                 230                 235                 240

eu Pro Tyr Leu Lys Gly Ile Cys Ser Gly Gly Gly Gly Asp Pro Glu
               245                 250                 255

rg Val Asp Arg Ser Ser Gln Arg Pro Gly Ala Glu Asp Asn Val Leu
           260                 265                 270

sn Glu Ile Val Ser Ile Leu Gln Pro Thr Gln Val Pro Glu Gln Glu
       275                 280                 285

et Glu Val Gln Glu Pro Ala Glu Pro Thr Gly Val Asn Met Leu Ser
   290                 295                 300

ro Gly Glu Ser Glu His Leu Leu Glu Pro Ala Glu Ala Glu Arg Ser
05                 310                 315                 320

n Arg Arg Arg Leu Leu Val Pro Ala Asn Glu Gly Asp Pro Thr Glu
               325                 330                 335

ir Leu Arg Gln Cys Phe Asp Asp Phe Ala Asp Leu Val Pro Phe Asp
           340                 345                 350

er Trp Glu Pro Leu Met Arg Lys Leu Gly Leu Met Asp Asn Glu Ile
       355                 360                 365

s Val Ala Lys Ala Glu Ala Ala Gly His Arg Asp Thr Leu Tyr Thr
   370                 375                 380

t Leu Ile Lys Trp Val Asn Lys Thr Gly Arg Asp Ala Ser Val His
5                  390                 395                 400

r Leu Leu Asp Ala Leu Glu Thr Leu Gly Glu Arg Leu Ala Lys Gln
               405                 410                 415
```

ys Ile Glu Asp His Leu Leu Ser Ser Gly Lys Phe Met Tyr Leu Glu
420 425 430

ly Asn Ala Asp Ser Ala Met Ser
435 440

210> 148
211> 126
212> PRT
213> Homo sapiens

400> 148

et Ala Asp Glu Ile Ala Lys Ala Gln Val Ala Arg Pro Gly Gly Asp
5 10 15

hr Ile Phe Gly Lys Ile Ile Arg Lys Glu Ile Pro Ala Lys Ile Ile
20 25 30

he Glu Asp Asp Arg Cys Leu Ala Phe His Asp Ile Ser Pro Gln Ala
35 40 45

ro Thr His Phe Leu Val Ile Pro Lys Lys His Ile Ser Gln Ile Ser
50 55 60

al Ala Glu Asp Asp Asp Glu Ser Leu Leu Gly His Leu Met Ile Val
5 70 75 80

ly Lys Lys Cys Ala Ala Asp Leu Gly Leu Asn Lys Gly Tyr Arg Met
85 90 95

al Val Asn Glu Gly Ser Asp Gly Gly Gln Ser Val Tyr His Val His
100 105 110

u His Val Leu Gly Gly Arg Gln Met His Trp Pro Pro Gly
115 120 125

10> 149
11> 320
12> PRT
13> Homo sapiens

00> 149

eolf-seql-S000001.txt

```
et Ala Glu Gly Asp Ala Gly Ser Asp Gln Arg Gln Asn Glu Glu Ile
               5                   10                  15

lu Ala Met Ala Ala Ile Tyr Gly Glu Glu Trp Cys Val Ile Asp Asp
           20                  25                  30

ys Ala Lys Ile Phe Cys Ile Arg Ile Ser Asp Asp Ile Asp Asp Pro
       35                  40                  45

ys Trp Thr Leu Cys Leu Gln Val Met Leu Pro Asn Glu Tyr Pro Gly
   50                  55                  60

hr Ala Pro Pro Ile Tyr Gln Leu Asn Ala Pro Trp Leu Lys Gly Gln
5                  70                  75                  80

lu Arg Ala Asp Leu Ser Asn Ser Leu Glu Glu Ile Tyr Ile Gln Asn
               85                  90                  95

le Gly Glu Ser Ile Leu Tyr Leu Trp Val Glu Lys Ile Arg Asp Val
           100                 105                 110

eu Ile Gln Lys Ser Gln Met Thr Glu Pro Gly Pro Asp Val Lys Lys
       115                 120                 125

ys Thr Glu Glu Glu Asp Val Glu Cys Glu Asp Asp Leu Ile Leu Ala
   130                 135                 140

ys Gln Pro Glu Ser Ser Val Lys Ala Leu Asp Phe Asp Ile Ser Glu
15                 150                 155                 160

ır Arg Thr Glu Val Glu Val Glu Glu Leu Pro Pro Ile Asp His Gly
               165                 170                 175

.e Pro Ile Thr Asp Arg Arg Ser Thr Phe Gln Ala His Leu Ala Pro
           180                 185                 190

ıl Val Cys Pro Lys Gln Val Lys Met Val Leu Ser Lys Leu Tyr Glu
       195                 200                 205

ın Lys Lys Ile Ala Ser Ala Thr His Asn Ile Tyr Ala Tyr Arg Ile
   210                 215                 220
```

eolf-seql-S000001.txt

yr Cys Glu Asp Lys Gln Thr Phe Leu Gln Asp Cys Glu Asp Asp Gly
25 230 235 240

lu Thr Ala Ala Gly Gly Arg Leu Leu His Leu Met Glu Ile Leu Asn
245 250 255

al Lys Asn Val Met Val Val Val Ser Arg Trp Tyr Gly Gly Ile Leu
260 265 270

eu Gly Pro Asp Arg Phe Lys His Ile Asn Asn Cys Ala Arg Asn Ile
275 280 285

eu Val Glu Lys Asn Tyr Thr Asn Ser Pro Glu Glu Ser Ser Lys Ala
290 295 300

eu Gly Lys Asn Lys Lys Val Arg Lys Asp Lys Lys Arg Asn Glu His
)5 310 315 320

210> 150
211> 326
212> PRT
213> Homo sapiens

400> 150

et His Arg Thr Thr Arg Ile Lys Ile Thr Glu Leu Asn Pro His Leu
5 10 15

et Cys Val Leu Cys Gly Gly Tyr Phe Ile Asp Ala Thr Thr Ile Ile
20 25 30

.u Cys Leu His Ser Phe Cys Lys Thr Cys Ile Val Arg Tyr Leu Glu
35 40 45

ır Ser Lys Tyr Cys Pro Ile Cys Asp Val Gln Val His Lys Thr Arg
50 55 60

'o Leu Leu Asn Ile Arg Ser Asp Lys Thr Leu Gln Asp Ile Val Tyr
70 75 80

's Leu Val Pro Gly Leu Phe Lys Asn Glu Met Lys Arg Arg Arg Asp
85 90 95

ne Tyr Ala Ala His Pro Ser Ala Asp Ala Ala Asn Gly Ser Asn Glu
100 105 110

sp Arg Gly Glu Val Ala Asp Glu Asp Lys Arg Ile Ile Thr Asp Asp
115 120 125

lu Ile Ile Ser Leu Ser Ile Glu Phe Phe Asp Gln Asn Arg Leu Asp
130 135 140

rg Lys Val Asn Lys Asp Lys Glu Lys Ser Lys Glu Glu Val Asn Asp
15 150 155 160

ys Arg Tyr Leu Arg Cys Pro Ala Ala Met Thr Val Met His Leu Arg
165 170 175

ys Phe Leu Arg Ser Lys Met Asp Ile Pro Asn Thr Phe Gln Ile Asp
180 185 190

al Met Tyr Glu Glu Glu Pro Leu Lys Asp Tyr Tyr Thr Leu Met Asp
195 200 205

.e Ala Tyr Ile Tyr Thr Trp Arg Arg Asn Gly Pro Leu Pro Leu Lys
210 215 220

'r Arg Val Arg Pro Thr Cys Lys Arg Met Lys Ile Ser His Gln Arg
:5 230 235 240

sp Gly Leu Thr Asn Ala Gly Glu Leu Glu Ser Asp Ser Gly Ser Asp
245 250 255

's Ala Asn Ser Pro Ala Gly Gly Ile Pro Ser Thr Ser Ser Cys Leu
260 265 270

o Ser Pro Ser Thr Pro Val Gln Ser Pro His Pro Gln Phe Pro His
275 280 285

e Ser Ser Thr Met Asn Gly Thr Ser Asn Ser Pro Ser Gly Asn His
290 295 300

n Ser Ser Phe Ala Asn Arg Pro Arg Lys Ser Ser Val Asn Gly Ser
5 310 315 320

er Ala Thr Ser Ser Gly
325

210> 151
211> 466
212> PRT
213> Homo sapiens

400> 151

et Val Met Glu Lys Pro Ser Pro Leu Leu Val Gly Arg Glu Phe Val
5 10 15

rg Gln Tyr Tyr Thr Leu Leu Asn Gln Ala Pro Asp Met Leu His Arg
20 25 30

ne Tyr Gly Lys Asn Ser Ser Tyr Val His Gly Gly Leu Asp Ser Asn
35 40 45

ly Lys Pro Ala Asp Ala Val Tyr Gly Gln Lys Glu Ile His Arg Lys
50 55 60

al Met Ser Gln Asn Phe Thr Asn Cys His Thr Lys Ile Arg His Val
5 70 75 80

sp Ala His Ala Thr Leu Asn Asp Gly Val Val Val Gln Val Met Gly
85 90 95

eu Leu Ser Asn Asn Asn Gln Ala Leu Arg Arg Phe Met Gln Thr Phe
100 105 110

al Leu Ala Pro Glu Gly Ser Val Ala Asn Lys Phe Tyr Val His Asn
115 120 125

sp Ile Phe Arg Tyr Gln Asp Glu Val Phe Gly Gly Phe Val Thr Glu
130 135 140

o Gln Glu Glu Ser Glu Glu Glu Val Glu Glu Pro Glu Glu Arg Gln
5 150 155 160

n Thr Pro Glu Val Val Pro Asp Asp Ser Gly Thr Phe Tyr Asp Gln
165 170 175

la Val Val Ser Asn Asp Met Glu Glu His Leu Glu Glu Pro Val Ala
180 185 190

lu Pro Glu Pro Asp Pro Glu Pro Glu Pro Glu Gln Glu Pro Val Ser
195 200 205

lu Ile Gln Glu Glu Lys Pro Glu Pro Val Leu Glu Glu Thr Ala Pro
210 215 220

lu Asp Ala Gln Lys Ser Ser Ser Pro Ala Pro Ala Asp Ile Ala Gln
25 230 235 240

ır Val Gln Glu Asp Leu Arg Thr Phe Ser Trp Ala Ser Val Thr Ser
245 250 255

/s Asn Leu Pro Pro Ser Gly Ala Val Pro Val Thr Gly Ile Pro Pro
260 265 270

.s Val Val Lys Val Pro Ala Ser Gln Pro Arg Pro Glu Ser Lys Pro
275 280 285

.u Ser Gln Ile Pro Pro Gln Arg Pro Gln Arg Asp Gln Arg Val Arg
290 295 300

.u Gln Arg Ile Asn Ile Pro Pro Gln Arg Gly Pro Arg Pro Ile Arg
)5 310 315 320

.u Ala Gly Glu Gln Gly Asp Ile Glu Pro Arg Arg Met Val Arg His
325 330 335

'o Asp Ser His Gln Leu Phe Ile Gly Asn Leu Pro His Glu Val Asp
340 345 350

's Ser Glu Leu Lys Asp Phe Phe Gln Ser Tyr Gly Asn Val.Val Glu
355 360 365

u Arg Ile Asn Ser Gly Gly Lys Leu Pro Asn Phe Gly Phe Val Val
370 375 380

e Asp Asp Ser Glu Pro Val Gln Lys Val Leu Ser Asn Arg Pro Ile

35 390 395 400

et Phe Arg Gly Glu Val Arg Leu Asn Val Glu Glu Lys Lys Thr Arg
405 410 415

la Ala Arg Glu Gly Asp Arg Arg Asp Asn Arg Leu Arg Gly Pro Gly
420 425 430

ly Pro Arg Gly Gly Leu Gly Gly Gly Met Arg Gly Pro Pro Arg Gly
435 440 445

ly Met Val Gln Lys Pro Gly Phe Gly Val Gly Arg Gly Leu Ala Pro
450 455 460

rg Gln
65

<210> 152
<211> 184
<212> PRT
<213> Homo sapiens

<400> 152

et Pro Gln Ser Lys Ser Arg Lys Ile Ala Ile Leu Gly Tyr Arg Ser
5 10 15

al Gly Lys Ser Ser Leu Thr Ile Gln Phe Val Glu Gly Gln Phe Val
20 25 30

sp Ser Tyr Asp Pro Thr Ile Glu Asn Thr Phe Thr Lys Leu Ile Thr
35 40 45

l Asn Gly Gln Glu Tyr His Leu Gln Leu Val Asp Thr Ala Gly Gln
50 55 60

p Glu Tyr Ser Ile Phe Pro Gln Thr Tyr Ser Ile Asp Ile Asn Gly
70 75 80

r Ile Leu Val Tyr Ser Val Thr Ser Ile Lys Ser Phe Glu Val Ile
85 90 95

s Val Ile His Gly Lys Leu Leu Asp Met Val Gly Lys Val Gln Ile

100 105 110

ro Ile Met Leu Val Gly Asn Lys Lys Asp Leu His Met Glu Arg Val
115 120 125

le Ser Tyr Glu Glu Gly Lys Ala Leu Ala Glu Ser Trp Asn Ala Ala
130 135 140

ne Leu Glu Ser Ser Ala Lys Glu Asn Gln Thr Ala Val Asp Val Phe
45 150 155 160

rg Arg Ile Ile Leu Glu Ala Glu Lys Met Asp Gly Ala Ala Ser Gln
165 170 175

Ly Lys Ser Ser Cys Ser Val Met
180

?10> 153
?11> 332
?12> PRT
?13> Homo sapiens

100> 153

:t Gly Ala Gln Phe Ser Lys Thr Ala Ala Lys Gly Glu Ala Ala Ala
5 10 15

.u Arg Pro Gly Glu Ala Ala Val Ala Ser Ser Pro Ser Lys Ala Asn
20 25 30

.y Gln Glu Asn Gly His Val Lys Val Asn Gly Asp Ala Ser Pro Ala
35 40 45

.a Ala Glu Ser Gly Ala Lys Glu Glu Leu Gln Ala Asn Gly Ser Ala
50 55 60

'o Ala Ala Asp Lys Glu Glu Pro Ala Ala Ala Gly Ser Gly Ala Ala
70 75 80

r Pro Ser Ser Ala Glu Lys Gly Glu Pro Ala Ala Ala Ala Ala Pro
85 90 95

u Ala Gly Ala Ser Pro Val Glu Lys Glu Ala Pro Ala Glu Gly Glu

100 105 110

la Ala Glu Pro Gly Ser Ala Thr Ala Ala Glu Gly Glu Ala Ala Ser
115 120 125

la Ala Ser Ser Thr Ser Ser Pro Lys Ala Glu Asp Gly Ala Thr Pro
130 135 140

er Pro Ser Asn Glu Thr Pro Lys Lys Lys Lys Lys Arg Phe Ser Phe
15 150 155 160

ys Lys Ser Phe Lys Leu Ser Gly Phe Ser Phe Lys Lys Asn Lys Lys
165 170 175

lu Ala Gly Glu Gly Gly Glu Ala Glu Ala Pro Ala Ala Glu Gly Gly
180 185 190

ys Asp Glu Ala Ala Gly Gly Ala Ala Ala Ala Ala Ala Glu Ala Gly
195 200 205

.a Ala Ser Gly Glu Gln Ala Ala Ala Pro Gly Glu Glu Ala Ala Ala
210 215 220

.y Glu Glu Gly Ala Ala Gly Gly Asp Pro Gln Glu Ala Lys Pro Gln
!5 230 235 240

.u Ala Ala Val Ala Pro Glu Lys Pro Pro Ala Ser Asp Glu Thr Lys
245 250 255

.a Ala Glu Glu Pro Ser Lys Val Glu Glu Lys Lys Ala Glu Glu Ala
260 265 270

y Ala Ser Ala Ala Ala Cys Glu Ala Pro Ser Ala Ala Gly Pro Gly
275 280 285

a Pro Pro Glu Gln Glu Ala Ala Pro Ala Glu Glu Pro Ala Ala Ala
290 295 300

a Ala Ser Ser Ala Cys Ala Ala Pro Ser Gln Glu Ala Gln Pro Glu
5 310 315 320

ys Ser Pro Glu Ala Pro Pro Ala Glu Ala Ala Glu
325 330

210> 154
211> 86
212> PRT
213> Homo sapiens

400> 154

et Pro Gln Tyr Gln Thr Trp Glu Glu Phe Ser Arg Ala Ala Glu Lys
5 10 15

eu Tyr Leu Ala Asp Pro Met Lys Ala Arg Val Val Leu Lys Tyr Arg
20 25 30

is Ser Asp Gly Asn Leu Cys Val Lys Val Thr Asp Asp Leu Val Cys
35 40 45

eu Val Tyr Lys Thr Asp Gln Ala Gln Asp Val Lys Lys Ile Glu Lys
50 55 60

he His Ser Gln Leu Met Arg Leu Met Val Ala Lys Glu Ala Arg Asn
5 70 75 80

al Thr Met Glu Thr Glu
85

10> 155
11> 480
12> PRT
13> Homo sapiens

00> 155

t Ile Arg Ala Ala Pro Pro Pro Leu Phe Leu Leu Leu Leu Leu Leu
5 10 15

u Leu Leu Val Ser Trp Ala Ser Arg Gly Glu Ala Ala Pro Asp Gln
20 25 30

p Glu Ile Gln Arg Leu Pro Gly Leu Ala Lys Gln Pro Ser Phe Arg
35 40 45

n Tyr Ser Gly Tyr Leu Lys Ser Ser Gly Ser Lys His Leu His Tyr

50 55 60

:p Phe Val Glu Ser Gln Lys Asp Pro Glu Asn Ser Pro Val Val Leu
; 70 75 80

:p Leu Asn Gly Gly Pro Gly Cys Ser Ser Leu Asp Gly Leu Leu Thr
85 90 95

.u His Gly Pro Phe Leu Val Gln Pro Asp Gly Val Thr Leu Glu Tyr
100 105 110

;n Pro Tyr Ser Trp Asn Leu Ile Ala Asn Val Leu Tyr Leu Glu Ser
115 120 125

:o Ala Gly Val Gly Phe Ser Tyr Ser Asp Asp Lys Phe Tyr Ala Thr
130 135 140

;n Asp Thr Glu Val Ala Gln Ser Asn Phe Glu Ala Leu Gln Asp Phe
:5 150 155 160

.e Arg Leu Phe Pro Glu Tyr Lys Asn Asn Lys Leu Phe Leu Thr Gly
165 170 175

u Ser Tyr Ala Gly Ile Tyr Ile Pro Thr Leu Ala Val Leu Val Met
180 185 190

n Asp Pro Ser Met Asn Leu Gln Gly Leu Ala Val Gly Asn Gly Leu
195 200 205

r Ser Tyr Glu Gln Asn Asp Asn Ser Leu Val Tyr Phe Ala Tyr Tyr
210 215 220

s Gly Leu Leu Gly Asn Arg Leu Trp Ser Ser Leu Gln Thr His Cys
5 230 235 240

s Ser Gln Asn Lys Cys Asn Phe Tyr Asp Asn Lys Asp Leu Glu Cys
245 250 255

l Thr Asn Leu Gln Glu Val Ala Arg Ile Val Gly Asn Ser Gly Leu
260 265 270

```
sn Ile Tyr Asn Leu Tyr Ala Pro Cys Ala Gly Gly Val Pro Ser His
       275                     280                     285

ne Arg Tyr Glu Lys Asp Thr Val Val Val Gln Asp Leu Gly Asn Ile
   290                     295                     300

ne Thr Arg Leu Pro Leu Lys Arg Met Trp His Gln Ala Leu Leu Arg
)5                     310                     315                     320

er Gly Asp Lys Val Arg Met Asp Pro Pro Cys Thr Asn Thr Thr Ala
                   325                     330                     335

.a Ser Thr Tyr Leu Asn Asn Pro Tyr Val Arg Lys Ala Leu Asn Ile
               340                     345                     350

:o Glu Gln Leu Pro Gln Trp Asp Met Cys Asn Phe Leu Val Asn Leu
       355                     360                     365

.n Tyr Arg Arg Leu Tyr Arg Ser Met Asn Ser Gln Tyr Leu Lys Leu
   370                     375                     380

:u Ser Ser Gln Lys Tyr Gln Ile Leu Leu Tyr Asn Gly Asp Val Asp
:5                     390                     395                     400

:t Ala Cys Asn Phe Met Gly Asp Glu Trp Phe Val Asp Ser Leu Asn
                   405                     410                     415

n Lys Met Glu Val Gln Arg Arg Pro Trp Leu Val Lys Tyr Gly Asp
               420                     425                     430

r Gly Glu Gln Ile Ala Gly Phe Val Lys Glu Phe Ser His Ile Ala
       435                     440                     445

e Leu Thr Ile Lys Gly Ala Gly His Met Val Pro Thr Asp Lys Pro
   450                     455                     460

u Ala Ala Phe Thr Met Phe Ser Arg Phe Leu Asn Lys Gln Pro Tyr
5                      470                     475                     480

10>  156
11>  217
12>  PRT
```

?13> Homo sapiens

?00> 156

?t Glu Ala Ile Ala Lys Tyr Asp Phe Lys Ala Thr Ala Asp Asp Glu
5 10 15

?u Ser Phe Lys Arg Gly Asp Ile Leu Lys Val Leu Asn Glu Glu Cys
20 25 30

?p Gln Asn Trp Tyr Lys Ala Glu Leu Asn Gly Lys Asp Gly Phe Ile
35 40 45

?o Lys Asn Tyr Ile Glu Met Lys Pro His Pro Trp Phe Phe Gly Lys
50 55 60

.e Pro Arg Ala Lys Ala Glu Glu Met Leu Ser Lys Gln Arg His Asp
; 70 75 80

.y Ala Phe Leu Ile Arg Glu Ser Glu Ser Ala Pro Gly Asp Phe Ser
85 90 95

?u Ser Val Lys Phe Gly Asn Asp Val Gln His Phe Lys Val Leu Arg
100 105 110

.p Gly Ala Gly Lys Tyr Phe Leu Trp Val Val Lys Phe Asn Ser Leu
115 120 125

n Glu Leu Val Asp Tyr His Arg Ser Thr Ser Val Ser Arg Asn Gln
130 135 140

n Ile Phe Leu Arg Asp Ile Glu Gln Val Pro Gln Gln Pro Thr Tyr
5 150 155 160

l Gln Ala Leu Phe Asp Phe Asp Pro Gln Glu Asp Gly Glu Leu Gly
165 170 175

e Arg Arg Gly Asp Phe Ile His Val Met Asp Asn Ser Asp Pro Asn
180 185 190

p Trp Lys Gly Ala Cys His Gly Gln Thr Gly Met Phe Pro Arg Asn
195 200 205

yr Val Thr Pro Val Asn Arg Asn Val
210 215

210> 157
211> 704
212> PRT
213> Homo sapiens

100> 157

et Ala Arg Glu Leu Arg Ala Leu Leu Leu Trp Gly Arg Arg Leu Arg
5 10 15

ro Leu Leu Arg Ala Pro Ala Leu Ala Ala Val Pro Gly Gly Lys Pro
20 25 30

.e Leu Cys Pro Arg Arg Thr Thr Ala Gln Leu Gly Pro Arg Arg Asn
35 40 45

ro Ala Trp Ser Leu Gln Ala Gly Arg Leu Phe Ser Thr Gln Thr Ala
50 55 60

.u Asp Lys Glu Glu Pro Leu His Ser Ile Ile Ser Ser Thr Glu Ser
5 70 75 80

il Gln Gly Ser Thr Ser Lys His Glu Phe Gln Ala Glu Thr Lys Lys
85 90 95

u Leu Asp Ile Val Ala Arg Ser Leu Tyr Ser Glu Lys Glu Val Phe
100 105 110

.e Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu Glu Lys Leu Arg
115 120 125

s Lys Leu Val Ser Asp Gly Gln Ala Leu Pro Glu Met Glu Ile His
130 135 140

u Gln Thr Asn Ala Glu Lys Gly Thr Ile Thr Ile Gln Asp Thr Gly
5 150 155 160

e Gly Met Thr Gln Glu Glu Leu Val Ser Asn Leu Gly Thr Ile Ala
165 170 175

eolf-seql-S000001.txt

```
rg Ser Gly Ser Lys Ala Phe Leu Asp Ala Leu Gln Asn Gln Ala Glu
           180                 185                 190

la Ser Ser Lys Ile Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala
       195                 200                 205

ne Met Val Ala Asp Arg Val Glu Val Tyr Ser Arg Ser Ala Ala Pro
   210                 215                 220

ly Ser Leu Gly Tyr Gln Trp Leu Ser Asp Gly Ser Gly Val Phe Glu
25                 230                 235                 240

.e Ala Glu Ala Ser Gly Val Arg Thr Gly Thr Lys Ile Ile Ile His
               245                 250                 255

eu Lys Ser Asp Cys Lys Glu Phe Ser Ser Glu Ala Arg Val Arg Asp
           260                 265                 270

al Val Thr Lys Tyr Ser Asn Phe Val Ser Phe Pro Leu Tyr Leu Asn
       275                 280                 285

.y Arg Arg Met Asn Thr Leu Gln Ala Ile Trp Met Met Asp Pro Lys
   290                 295                 300

sp Val Gly Glu Trp Gln His Glu Glu Phe Tyr Arg Tyr Val Ala Gln
5                  310                 315                 320

.a His Asp Lys Pro Arg Tyr Thr Leu His Tyr Lys Thr Asp Ala Pro
               325                 330                 335

u Asn Ile Arg Ser Ile Phe Tyr Val Pro Asp Met Lys Pro Ser Met
           340                 345                 350

e Asp Val Ser Arg Glu Leu Gly Ser Ser Val Ala Leu Tyr Ser Arg
       355                 360                 365

s Val Leu Ile Gln Thr Lys Ala Thr Asp Ile Leu Pro Lys Trp Leu
   370                 375                 380

g Phe Ile Arg Gly Val Val Asp Ser Glu Asp Ile Pro Leu Asn Leu
5                  390                 395                 400
```

```
er Arg Glu Leu Leu Gln Glu Ser Ala Leu Ile Arg Lys Leu Arg Asp
                   405                 410                 415

al Leu Gln Gln Arg Leu Ile Lys Phe Phe Ile Asp Gln Ser Lys Lys
               420                 425                 430

sp Ala Glu Lys Tyr Ala Lys Phe Phe Glu Asp Tyr Gly Leu Phe Met
           435                 440                 445

rg Glu Gly Ile Val Thr Ala Thr Glu Gln Glu Val Lys Glu Asp Ile
       450                 455                 460

la Lys Leu Leu Arg Tyr Glu Ser Ser Ala Leu Pro Ser Gly Gln Leu
65                     470                 475                 480

hr Ser Leu Ser Glu Tyr Ala Ser Arg Met Arg Ala Gly Thr Arg Asn
                   485                 490                 495

le Tyr Tyr Leu Cys Ala Pro Asn Arg His Leu Ala Glu His Ser Pro
               500                 505                 510

r Tyr Glu Ala Met Lys Lys Lys Asp Thr Glu Val Leu Phe Cys Phe
          515                 520                 525

u Gln Phe Asp Glu Leu Thr Leu Leu His Leu Arg Glu Phe Asp Lys
   530                 535                 540

s Lys Leu Ile Ser Val Glu Thr Asp Ile Val Val Asp His Tyr Lys
5                     550                 555                 560

u Glu Lys Phe Glu Asp Arg Ser Pro Ala Ala Glu Cys Leu Ser Glu
                  565                 570                 575

s Glu Thr Glu Glu Leu Met Ala Trp Met Arg Asn Val Leu Gly Ser
              580                 585                 590

g Val Thr Asn Val Lys Val Thr Leu Arg Leu Asp Thr His Pro Ala
          595                 600                 605

t Val Thr Val Leu Glu Met Gly Ala Ala Arg His Phe Leu Arg Met
```

610 615 620

ln Gln Leu Ala Lys Thr Gln Glu Glu Arg Ala Gln Leu Leu Gln Pro
25 630 635 640

hr Leu Glu Ile Asn Pro Arg His Ala Leu Ile Lys Lys Leu Asn Gln
645 650 655

eu Arg Ala Ser Glu Pro Gly Leu Ala Gln Leu Leu Val Asp Gln Ile
660 665 670

yr Glu Asn Ala Met Ile Ala Ala Gly Leu Val Asp Asp Pro Arg Ala
675 680 685

et Val Gly Arg Leu Asn Glu Leu Leu Val Lys Ala Leu Glu Arg His
690 695 700

:10> 158
:11> 359
:12> PRT
:13> Homo sapiens

·00> 158

·t Ala Ala Val Ser Gly Leu Val Arg Arg Pro Leu Arg Glu Val Ser
5 10 15

y Leu Leu Lys Arg Arg Phe His Trp Thr Ala Pro Ala Ala Leu Gln
20 25 30

l Thr Val Arg Asp Ala Ile Asn Gln Gly Met Asp Glu Glu Leu Glu
35 40 45

g Asp Glu Lys Val Phe Leu Leu Gly Glu Glu Val Ala Gln Tyr Asp
50 55 60

y Ala Tyr Lys Val Ser Arg Gly Leu Trp Lys Lys Tyr Gly Asp Lys
70 75 80

y Ile Ile Asp Thr Pro Ile Ser Glu Met Gly Phe Ala Gly Ile Ala
85 90 95

. Gly Ala Ala Met Ala Gly Leu Arg Pro Ile Cys Glu Phe Met Thr

100 105 110

ne Asn Phe Ser Met Gln Ala Ile Asp Gln Val Ile Asn Ser Ala Ala
115 120 125

ys Thr Tyr Tyr Met Ser Gly Gly Leu Gln Pro Val Pro Ile Val Phe
130 135 140

rg Gly Pro Asn Gly Ala Ser Ala Gly Val Ala Ala Gln His Ser Gln
45 150 155 160

ys Phe Ala Ala Trp Tyr Gly His Cys Pro Gly Leu Lys Val Val Ser
165 170 175

ro Trp Asn Ser Glu Asp Ala Lys Gly Leu Ile Lys Ser Ala Ile Arg
180 185 190

sp Asn Asn Pro Val Val Val Leu Glu Asn Glu Leu Met Tyr Gly Val
195 200 205

ro Phe Glu Phe Leu Pro Glu Ala Gln Ser Lys Asp Phe Leu Ile Pro
210 215 220

le Gly Lys Ala Lys Ile Glu Arg Gln Gly Thr His Ile Thr Val Val
25 230 235 240

er His Ser Arg Pro Val Gly His Cys Leu Glu Ala Ala Ala Val Leu
245 250 255

er Lys Glu Gly Val Glu Cys Glu Val Ile Asn Met Arg Thr Ile Arg
260 265 270

o Met Asp Met Glu Thr Ile Glu Ala Ser Val Met Lys Thr Asn His
275 280 285

u Val Thr Val Glu Gly Gly Trp Pro Gln Phe Gly Val Gly Ala Glu
290 295 300

e Cys Ala Arg Ile Met Glu Gly Pro Ala Phe Asn Phe Leu Asp Ala
5 310 315 320

:o Ala Val Arg Val Thr Gly Ala Asp Val Pro Met Pro Tyr Ala Lys
325 330 335

.e Leu Glu Asp Asn Ser Ile Pro Gln Val Lys Asp Ile Ile Phe Ala
340 345 350

.e Lys Lys Thr Leu Asn Ile
355

:10> 159
:11> 113
:12> PRT
:13> Homo sapiens

00> 159

:t Ser Ala Ser Val Val Ser Val Ile Ser Arg Phe Leu Glu Glu Tyr
5 10 15

·u Ser Ser Thr Pro Gln Arg Leu Lys Leu Leu Asp Ala Tyr Leu Leu
20 25 30

·r Ile Leu Leu Thr Gly Ala Leu Gln Phe Gly Tyr Cys Leu Leu Val
35 40 45

y Thr Phe Pro Phe Asn Ser Phe Leu Ser Gly Phe Ile Ser Cys Val
50 55 60

y Ser Phe Ile Leu Ala Val Cys Leu Arg Ile Gln Ile Asn Pro Gln
70 75 80

n Lys Ala Asp Phe Gln Gly Ile Ser Pro Glu Arg Ala Phe Ala Asp
85 90 95

e Leu Phe Ala Ser Thr Ile Leu His Leu Val Val Met Asn Phe Val
100 105 110

y

10> 160
11> 239
12> PRT
13> Homo sapiens

400> 160

et Ala Lys Pro Cys Gly Val Arg Leu Ser Gly Glu Ala Arg Lys Gln
5 10 15

al Glu Val Phe Arg Gln Asn Leu Phe Gln Glu Ala Glu Glu Phe Leu
20 25 30

yr Arg Phe Leu Pro Gln Lys Ile Ile Tyr Leu Asn Gln Leu Leu Gln
35 40 45

lu Asp Ser Leu Asn Val Ala Asp Leu Thr Ser Leu Arg Ala Pro Leu
50 55 60

sp Ile Pro Ile Pro Asp Pro Pro Pro Lys Asp Asp Glu Met Glu Thr
5 70 75 80

sp Lys Gln Glu Lys Lys Glu Val His Lys Cys Gly Phe Leu Pro Gly
85 90 95

sn Glu Lys Val Leu Ser Leu Leu Ala Leu Val Lys Pro Glu Val Trp
100 105 110

ır Leu Lys Glu Lys Cys Ile Leu Val Ile Thr Trp Ile Gln His Leu
115 120 125

.e Pro Lys Ile Glu Asp Gly Asn Asp Phe Gly Val Ala Ile Gln Glu
130 135 140

's Val Leu Glu Arg Val Asn Ala Val Lys Thr Lys Val Glu Ala Phe
5 150 155 160

n Thr Thr Ile Ser Lys Tyr Phe Ser Glu Arg Gly Asp Ala Val Ala
165 170 175

s Ala Ser Lys Glu Thr His Val Met Asp Tyr Arg Ala Leu Val His
180 185 190

u Arg Asp Glu Ala Ala Tyr Gly Glu Leu Arg Ala Met Val Leu Asp
195 200 205

eu Arg Ala Phe Tyr Ala Glu Leu Tyr His Ile Ile Ser Ser Asn Leu
210 215 220

lu Lys Ile Val Asn Pro Lys Gly Glu Glu Lys Pro Ser Met Tyr
25 230 235

210> 161
211> 111
212> PRT
213> Homo sapiens

100> 161

et Ala Gly Lys Gln Ala Val Ser Ala Ser Gly Lys Trp Leu Asp Gly
5 10 15

.e Arg Lys Trp Tyr Tyr Asn Ala Ala Gly Phe Asn Lys Leu Gly Leu
20 25 30

et Arg Asp Asp Thr Ile Tyr Glu Asp Glu Asp Val Lys Glu Ala Ile
35 40 45

g Arg Leu Pro Glu Asn Leu Tyr Asn Asp Arg Met Phe Arg Ile Lys
50 55 60

g Ala Leu Asp Leu Asn Leu Lys His Gln Ile Leu Pro Lys Glu Gln
70 75 80

p Thr Lys Tyr Glu Glu Glu Asn Phe Tyr Leu Glu Pro Tyr Leu Lys
85 90 95

u Val Ile Arg Glu Arg Lys Glu Arg Glu Glu Trp Ala Lys Lys
100 105 110

10> 162
11> 106
12> PRT
13> Homo sapiens

00> 162

t Ser Ser Leu Ser Glu Tyr Ala Phe Arg Met Ser Arg Leu Ser Ala
5 10 15

g Leu Phe Gly Glu Val Thr Arg Pro Thr Asn Ser Lys Ser Met Lys

20 25 30

al Val Lys Leu Phe Ser Glu Leu Pro Leu Ala Lys Lys Lys Glu Thr
35 40 45

yr Asp Trp Tyr Pro Asn His His Thr Tyr Ala Glu Leu Met Gln Thr
50 55 60

eu Arg Phe Leu Gly Leu Tyr Arg Asp Glu His Gln Asp Phe Met Asp
5 70 75 80

lu Gln Lys Arg Leu Lys Lys Leu Arg Gly Lys Glu Lys Pro Lys Lys
85 90 95

ly Glu Gly Lys Arg Ala Ala Lys Arg Lys
100 105

:10> 163
:11> 180
:12> PRT
:13> Homo sapiens

100> 163

et Gly Leu Thr Ile Ser Ser Leu Phe Ser Arg Leu Phe Gly Lys Lys
5 10 15

.n Met Arg Ile Leu Met Val Gly Leu Asp Ala Ala Gly Lys Thr Thr
20 25 30

.e Leu Tyr Lys Leu Lys Leu Gly Glu Ile Val Thr Thr Ile Pro Thr
35 40 45

.e Gly Phe Asn Val Glu Thr Val Glu Tyr Lys Asn Ile Cys Phe Thr
50 55 60

l Trp Asp Val Gly Gly Gln Asp Arg Ile Arg Pro Leu Trp Lys His
70 75 80

r Phe Gln Asn Thr Gln Gly Leu Ile Phe Val Val Asp Ser Asn Asp
85 90 95

g Glu Arg Ile Gln Glu Val Ala Asp Glu Leu Gln Lys Met Leu Leu

100 105 110

al Asp Glu Leu Arg Asp Ala Val Leu Leu Leu Phe Ala Asn Lys Gln
115 120 125

sp Leu Pro Asn Ala Met Ala Ile Ser Glu Met Thr Asp Lys Leu Gly
130 135 140

eu Gln Ser Leu Arg Asn Arg Thr Trp Tyr Val Gln Ala Thr Cys Ala
15 150 155 160

ır Gln Gly Thr Gly Leu Tyr Glu Gly Leu Asp Trp Leu Ser Asn Glu
165 170 175

eu Ser Lys Arg
180

:10> 164
:11> 1140
:12> PRT
:13> Homo sapiens

.00> 164

:t Ser Tyr Asn Tyr Val Val Thr Ala Gln Lys Pro Thr Ala Val Asn
5 10 15

y Cys Val Thr Gly His Phe Thr Ser Ala Glu Asp Leu Asn Leu Leu
20 25 30

e Ala Lys Asn Thr Arg Leu Glu Ile Tyr Val Val Thr Ala Glu Gly
35 40 45

u Arg Pro Val Lys Glu Val Gly Met Tyr Gly Lys Ile Ala Val Met
50 55 60

u Leu Phe Arg Pro Lys Gly Glu Ser Lys Asp Leu Leu Phe Ile Leu
70 75 80

r Ala Lys Tyr Asn Ala Cys Ile Leu Glu Tyr Lys Gln Ser Gly Glu
85 90 95

r Ile Asp Ile Ile Thr Arg Ala His Gly Asn Val Gln Asp Arg Ile

100 105 110

Ly Arg Pro Ser Glu Thr Gly Ile Ile Gly Ile Ile Asp Pro Glu Cys
115 120 125

:g Met Ile Gly Leu Arg Leu Tyr Asp Gly Leu Phe Lys Val Ile Pro
130 135 140

:u Asp Arg Asp Asn Lys Glu Leu Lys Ala Phe Asn Ile Arg Leu Glu
15 150 155 160

.u Leu His Val Ile Asp Val Lys Phe Leu Tyr Gly Cys Gln Ala Pro
165 170 175

ır Ile Cys Phe Val Tyr Gln Asp Pro Gln Gly Arg His Val Lys Thr
180 185 190

'r Glu Val Ser Leu Arg Glu Lys Glu Phe Asn Lys Gly Pro Trp Lys
195 200 205

.n Glu Asn Val Glu Ala Glu Ala Ser Met Val Ile Ala Val Pro Glu
210 215 220

'o Phe Gly Gly Ala Ile Ile Ile Gly Gln Glu Ser Ile Thr Tyr His
5 230 235 240

n Gly Asp Lys Tyr Leu Ala Ile Ala Pro Pro Ile Ile Lys Gln Ser
245 250 255

.r Ile Val Cys His Asn Arg Val Asp Pro Asn Gly Ser Arg Tyr Leu
260 265 270

u Gly Asp Met Glu Gly Arg Leu Phe Met Leu Leu Leu Glu Lys Glu
275 280 285

u Gln Met Asp Gly Thr Val Thr Leu Lys Asp Leu Arg Val Glu Leu
290 295 300

u Gly Glu Thr Ser Ile Ala Glu Cys Leu Thr Tyr Leu Asp Asn Gly
5 310 315 320

eolf-seql-S000001.txt

```
il Val Phe Val Gly Ser Arg Leu Gly Asp Ser Gln Leu Val Lys Leu
                   325                 330                 335

sn Val Asp Ser Asn Glu Gln Gly Ser Tyr Val Val Ala Met Glu Thr
               340                 345                 350

ie Thr Asn Leu Gly Pro Ile Val Asp Met Cys Val Val Asp Leu Glu
           355                 360                 365

:g Gln Gly Gln Gly Gln Leu Val Thr Cys Ser Gly Ala Phe Lys Glu
   370                 375                 380

.y Ser Leu Arg Ile Ile Arg Asn Gly Ile Gly Ile His Glu His Ala
:5                     390                 395                 400

:r Ile Asp Leu Pro Gly Ile Lys Gly Leu Trp Pro Leu Arg Ser Asp
                   405                 410                 415

o Asn Arg Glu Thr Tyr Asp Thr Leu Val Leu Ser Phe Val Gly Gln
               420                 425                 430

r Arg Val Leu Met Leu Asn Gly Glu Glu Val Glu Glu Thr Glu Leu
           435                 440                 445

t Gly Phe Val Asp Asp Gln Gln Thr Phe Phe Cys Gly Asn Val Ala
   450                 455                 460

s Gln Gln Leu Ile Gln Ile Thr Ser Ala Ser Val Arg Leu Val Ser
5                      470                 475                 480

n Glu Pro Lys Ala Leu Val Ser Glu Trp Lys Glu Pro Gln Ala Lys
                   485                 490                 495

n Ile Ser Val Ala Ser Cys Asn Ser Ser Gln Val Val Val Ala Val
               500                 505                 510

y Arg Ala Leu Tyr Tyr Leu Gln Ile His Pro Gln Glu Leu Arg Gln
           515                 520                 525

e Ser His Thr Glu Met Glu His Glu Val Ala Cys Leu Asp Ile Thr
   530                 535                 540
```

ro Leu Gly Asp Ser Asn Gly Leu Ser Pro Leu Cys Ala Ile Gly Leu
45 550 555 560

rp Thr Asp Ile Ser Ala Arg Ile Leu Lys Leu Pro Ser Phe Glu Leu
565 570 575

eu His Lys Glu Met Leu Gly Gly Glu Ile Ile Pro Arg Ser Ile Leu
580 585 590

et Thr Thr Phe Glu Ser Ser His Tyr Leu Leu Cys Ala Leu Gly Asp
595 600 605

ly Ala Leu Phe Tyr Phe Gly Leu Asn Ile Glu Thr Gly Leu Leu Ser
610 615 620

sp Arg Lys Lys Val Thr Leu Gly Thr Gln Pro Thr Val Leu Arg Thr
25 630 635 640

ne Arg Ser Leu Ser Thr Thr Asn Val Phe Ala Cys Ser Asp Arg Pro
645 650 655

ir Val Ile Tyr Ser Ser Asn His Lys Leu Val Phe Ser Asn Val Asn
660 665 670

eu Lys Glu Val Asn Tyr Met Cys Pro Leu Asn Ser Asp Gly Tyr Pro
675 680 685

sp Ser Leu Ala Leu Ala Asn Asn Ser Thr Leu Thr Ile Gly Thr Ile
690 695 700

p Glu Ile Gln Lys Leu His Ile Arg Thr Val Pro Leu Tyr Glu Ser
5 710 715 720

o Arg Lys Ile Cys Tyr Gln Glu Val Ser Gln Cys Phe Gly Val Leu
725 730 735

r Ser Arg Ile Glu Val Gln Asp Thr Ser Gly Gly Thr Thr Ala Leu
740 745 750

g Pro Ser Ala Ser Thr Gln Ala Leu Ser Ser Ser Val Ser Ser Ser
755 760 765

ys Leu Phe Ser Ser Ser Thr Ala Pro His Glu Thr Ser Phe Gly Glu
770 775 780

lu Val Glu Val His Asn Leu Leu Ile Ile Asp Gln His Thr Phe Glu
35 790 795 800

al Leu His Ala His Gln Phe Leu Gln Asn Glu Tyr Ala Leu Ser Leu
805 810 815

al Ser Cys Lys Leu Gly Lys Asp Pro Asn Thr Tyr Phe Ile Val Gly
820 825 830

ır Ala Met Val Tyr Pro Glu Glu Ala Glu Pro Lys Gln Gly Arg Ile
835 840 845

al Val Phe Gln Tyr Ser Asp Gly Lys Leu Gln Thr Val Ala Glu Lys
850 855 860

.u Val Lys Gly Ala Val Tyr Ser Met Val Glu Phe Asn Gly Lys Leu
55 870 875 880

:u Ala Ser Ile Asn Ser Thr Val Arg Leu Tyr Glu Trp Thr Thr Glu
885 890 895

'S Asp Val Arg Thr Glu Cys Asn His Tyr Asn Asn Ile Met Ala Leu
900 905 910

'r Leu Lys Thr Lys Gly Asp Phe Ile Leu Val Gly Asp Leu Met Arg
915 920 925

:r Val Leu Leu Leu Ala Tyr Lys Pro Met Glu Gly Asn Phe Glu Glu
930 935 940

e Ala Arg Asp Phe Asn Pro Asn Trp Met Ser Ala Val Glu Ile Leu
5 950 955 960

p Asp Asp Asn Phe Leu Gly Ala Glu Asn Ala Phe Asn Leu Phe Val
965 970 975

s Gln Lys Asp Ser Ala Ala Thr Thr Asp Glu Glu Arg Gln His Leu

980 985 990

ln Glu Val Gly Leu Phe His Leu Gly Glu Phe Val Asn Val Phe Cys
995 1000 1005

is Gly Ser Leu Val Met Gln Asn Leu Gly Glu Thr Ser Thr Pro
1010 1015 1020

ır Gln Gly Ser Val Leu Phe Gly Thr Val Asn Gly Met Ile Gly
1025 1030 1035

eu Val Thr Ser Leu Ser Glu Ser Trp Tyr Asn Leu Leu Leu Asp
1040 1045 1050

et Gln Asn Arg Leu Asn Lys Val Ile Lys Ser Val Gly Lys Ile
1055 1060 1065

lu His Ser Phe Trp Arg Ser Phe His Thr Glu Arg Lys Thr Glu
1070 1075 1080

ro Ala Thr Gly Phe Ile Asp Gly Asp Leu Ile Glu Ser Phe Leu
1085 1090 1095

sp Ile Ser Arg Pro Lys Met Gln Glu Val Val Ala Asn Leu Gln
1100 1105 1110

yr Asp Asp Gly Ser Gly Met Lys Arg Glu Ala Thr Ala Asp Asp
1115 1120 1125

eu Ile Lys Val Val Glu Glu Leu Thr Arg Ile His
1130 1135 1140

:10> 165
:11> 153
:12> PRT
:13> Homo sapiens

00> 165

t Gly Ala Pro Leu Leu Ser Pro Gly Trp Gly Ala Gly Ala Ala Gly
5 10 15

g Arg Trp Trp Met Leu Leu Ala Pro Leu Leu Pro Ala Leu Leu Leu

20 25 30

al Arg Pro Ala Gly Ala Leu Val Glu Gly Leu Tyr Cys Gly Thr Arg
35 40 45

sp Cys Tyr Glu Val Leu Gly Val Ser Arg Ser Ala Gly Lys Ala Glu
50 55 60

.e Ala Arg Ala Tyr Arg Gln Leu Ala Arg Arg Tyr His Pro Asp Arg
5 70 75 80

'r Arg Pro Gln Pro Gly Asp Glu Gly Pro Gly Arg Thr Pro Gln Ser
85 90 95

.a Glu Glu Ala Phe Leu Leu Val Ala Thr Ala Tyr Glu Thr Leu Lys
100 105 110

ıl Ser Gln Ala Ala Ala Glu Leu Gln Gln Tyr Cys Met Gln Asn Ala
115 120 125

's Lys Asp Ala Leu Leu Val Gly Val Pro Ala Gly Ser Asn Pro Phe
130 135 140

'g Glu Pro Arg Ser Cys Ala Leu Leu
5 150

10> 166
11> 557
12> PRT
13> Homo sapiens

00> 166

t Asp Gly Ile Val Pro Asp Ile Ala Val Gly Thr Lys Arg Gly Ser
5 10 15

p Glu Leu Phe Ser Thr Cys Val Thr Asn Gly Pro Phe Ile Met Ser
20 25 30

r Asn Ser Ala Ser Ala Ala Asn Gly Asn Asp Ser Lys Lys Phe Lys
35 40 45

y Asp Ser Arg Ser Ala Gly Val Pro Ser Arg Val Ile His Ile Arg

50 55 60

ys Leu Pro Ile Asp Val Thr Glu Gly Glu Val Ile Ser Leu Gly Leu
5 70 75 80

ro Phe Gly Lys Val Thr Asn Leu Leu Met Leu Lys Gly Lys Asn Gln
85 90 95

la Phe Ile Glu Met Asn Thr Glu Glu Ala Ala Asn Thr Met Val Asn
100 105 110

yr Tyr Thr Ser Val Thr Pro Val Leu Arg Gly Gln Pro Ile Tyr Ile
115 120 125

ln Phe Ser Asn His Lys Glu Leu Lys Thr Asp Ser Ser Pro Asn Gln
130 135 140

la Arg Ala Gln Ala Ala Leu Gln Ala Val Asn Ser Val Gln Ser Gly
15 150 155 160

sn Leu Ala Leu Ala Ala Ser Ala Ala Ala Val Asp Ala Gly Met Ala
165 170 175

et Ala Gly Gln Ser Pro Val Leu Arg Ile Ile Val Glu Asn Leu Phe
180 185 190

r Pro Val Thr Leu Asp Val Leu His Gln Ile Phe Ser Lys Phe Gly
195 200 205

ır Val Leu Lys Ile Ile Thr Phe Thr Lys Asn Asn Gln Phe Gln Ala
210 215 220

u Leu Gln Tyr Ala Asp Pro Val Ser Ala Gln His Ala Lys Leu Ser
5 230 235 240

u Asp Gly Gln Asn Ile Tyr Asn Ala Cys Cys Thr Leu Arg Ile Asp
245 250 255

e Ser Lys Leu Thr Ser Leu Asn Val Lys Tyr Asn Asn Asp Lys Ser
260 265 270

:g Asp Tyr Thr Arg Pro Asp Leu Pro Ser Gly Asp Ser Gln Pro Ser
275 280 285

eu Asp Gln Thr Met Ala Ala Ala Phe Gly Ala Pro Gly Ile Ile Ser
290 295 300

.a Ser Pro Tyr Ala Gly Ala Gly Phe Pro Pro Thr Phe Ala Ile Pro
)5 310 315 320

.n Ala Ala Gly Leu Ser Val Pro Asn Val His Gly Ala Leu Ala Pro
325 330 335

eu Ala Ile Pro Ser Ala Ala Ala Ala Ala Ala Ala Ala Gly Arg Ile
340 345 350

.a Ile Pro Gly Leu Ala Gly Ala Gly Asn Ser Val Leu Leu Val Ser
355 360 365

:n Leu Asn Pro Glu Arg Val Thr Pro Gln Ser Leu Phe Ile Leu Phe
370 375 380

.y Val Tyr Gly Asp Val Gln Arg Val Lys Ile Leu Phe Asn Lys Lys
.5 390 395 400

u Asn Ala Leu Val Gln Met Ala Asp Gly Asn Gln Ala Gln Leu Ala
405 410 415

t Ser His Leu Asn Gly His Lys Leu His Gly Lys Pro Ile Arg Ile
420 425 430

r Leu Ser Lys His Gln Asn Val Gln Leu Pro Arg Glu Gly Gln Glu
435 440 445

p Gln Gly Leu Thr Lys Asp Tyr Gly Asn Ser Pro Leu His Arg Phe
450 455 460

s Lys Pro Gly Ser Lys Asn Phe Gln Asn Ile Phe Pro Pro Ser Ala
5 470 475 480

r Leu His Leu Ser Asn Ile Pro Pro Ser Val Ser Glu Glu Asp Leu
485 490 495

’s Val Leu Phe Ser Ser Asn Gly Gly Val Val Lys Gly Phe Lys Phe
500 505 510

ıe Gln Lys Asp Arg Lys Met Ala Leu Ile Gln Met Gly Ser Val Glu
515 520 525

.u Ala Val Gln Ala Leu Ile Asp Leu His Asn His Asp Leu Gly Glu
530 535 540

;n His His Leu Arg Val Ser Phe Ser Lys Ser Thr Ile
ı5 550 555

:10> 167
:11> 303
:12> PRT
:13> Homo sapiens

:00> 167

:t Ala Arg Gly Lys Ala Lys Glu Glu Gly Ser Trp Lys Lys Phe Ile
5 10 15

'p Asn Ser Glu Lys Lys Glu Phe Leu Gly Arg Thr Gly Gly Ser Trp
20 25 30

.e Lys Ile Leu Leu Phe Tyr Val Ile Phe Tyr Gly Cys Leu Ala Gly
35 40 45

e Phe Ile Gly Thr Ile Gln Val Met Leu Leu Thr Ile Ser Glu Phe
50 55 60

s Pro Thr Tyr Gln Asp Arg Val Ala Pro Pro Gly Leu Thr Gln Ile
70 75 80

o Gln Ile Gln Lys Thr Glu Ile Ser Phe Arg Pro Asn Asp Pro Lys
85 90 95

r Tyr Glu Ala Tyr Val Leu Asn Ile Val Arg Phe Leu Glu Lys Tyr
100 105 110

s Asp Ser Ala Gln Arg Asp Asp Met Ile Phe Glu Asp Cys Gly Asp
115 120 125

```
al Pro Ser Glu Pro Lys Glu Arg Gly Asp Phe Asn His Glu Arg Gly
    130                 135                 140

lu Arg Lys Val Cys Arg Phe Lys Leu Glu Trp Leu Gly Asn Cys Ser
15                  150                 155                 160

.y Leu Asn Asp Glu Thr Tyr Gly Tyr Lys Glu Gly Lys Pro Cys Ile
                165                 170                 175

.e Ile Lys Leu Asn Arg Val Leu Gly Phe Lys Pro Lys Pro Pro Lys
            180                 185                 190

sn Glu Ser Leu Glu Thr Tyr Pro Val Met Lys Tyr Asn Pro Asn Val
        195                 200                 205

:u Pro Val Gln Cys Thr Gly Lys Arg Asp Glu Asp Lys Asp Lys Val
    210                 215                 220

.y Asn Val Glu Tyr Phe Gly Leu Gly Asn Ser Pro Gly Phe Pro Leu
:5                  230                 235                 240

.n Tyr Tyr Pro Tyr Tyr Gly Lys Leu Leu Gln Pro Lys Tyr Leu Gln
                245                 250                 255

o Leu Leu Ala Val Gln Phe Thr Asn Leu Thr Met Asp Thr Glu Ile
            260                 265                 270

g Ile Glu Cys Lys Ala Tyr Gly Glu Asn Ile Gly Tyr Ser Glu Lys
        275                 280                 285

p Arg Phe Gln Gly Arg Phe Asp Val Lys Ile Glu Val Lys Ser
    290                 295                 300


10>  168
11>  361
12>  PRT
13>  Homo sapiens

00>  168

t Phe Ser Ser Val Ala His Leu Ala Arg Ala Asn Pro Phe Asn Thr
                5                   10                  15
```

:o His Leu Gln Leu Val His Asp Gly Leu Gly Asp Leu Arg Ser Ser
20 25 30

er Pro Gly Pro Thr Gly Gln Pro Arg Arg Pro Arg Asn Leu Ala Ala
35 40 45

La Ala Val Glu Glu Tyr Ser Cys Glu Phe Gly Ser Ala Lys Tyr Tyr
50 55 60

.a Leu Cys Gly Phe Gly Gly Val Leu Ser Cys Gly Leu Thr His Thr
5 70 75 80

.a Val Val Pro Leu Asp Leu Val Lys Cys Arg Met Gln Val Asp Pro
85 90 95

.n Lys Tyr Lys Gly Ile Phe Asn Gly Phe Ser Val Thr Leu Lys Glu
100 105 110

;p Gly Val Arg Gly Leu Ala Lys Gly Trp Ala Pro Thr Phe Leu Gly
115 120 125

'r Ser Met Gln Gly Leu Cys Lys Phe Gly Phe Tyr Glu Val Phe Lys
130 135 140

.l Leu Tyr Ser Asn Met Leu Gly Glu Glu Asn Thr Tyr Leu Trp Arg
5 150 155 160

.r Ser Leu Tyr Leu Ala Ala Ser Ala Ser Ala Glu Phe Phe Ala Asp
165 170 175

e Ala Leu Ala Pro Met Glu Ala Ala Lys Val Arg Ile Gln Thr Gln
180 185 190

o Gly Tyr Ala Asn Thr Leu Arg Asp Ala Ala Pro Lys Met Tyr Lys
195 200 205

u Glu Gly Leu Lys Ala Phe Tyr Lys Gly Val Ala Pro Leu Trp Met
210 215 220

g Gln Ile Pro Tyr Thr Met Met Lys Phe Ala Cys Phe Glu Arg Thr
5 230 235 240

al Glu Ala Leu Tyr Lys Phe Val Val Pro Lys Pro Arg Ser Glu Cys
245 250 255

er Lys Pro Glu Gln Leu Val Val Thr Phe Val Ala Gly Tyr Ile Ala
260 265 270

.y Val Phe Cys Ala Ile Val Ser His Pro Ala Asp Ser Val Val Ser
275 280 285

ıl Leu Asn Lys Glu Lys Gly Ser Ser Ala Ser Leu Val Leu Lys Arg
290 295 300

eu Gly Phe Lys Gly Val Trp Lys Gly Leu Phe Ala Arg Ile Ile Met
)5 310 315 320

.e Gly Thr Leu Thr Ala Leu Gln Trp Phe Ile Tyr Asp Ser Val Lys
325 330 335

ıl Tyr Phe Arg Leu Pro Arg Pro Pro Pro Pro Glu Met Pro Glu Ser
340 345 350

u Lys Lys Lys Leu Gly Leu Thr Gln
355 360

10> 169
11> 369
12> PRT
13> Homo sapiens

00> 169

t Asp Pro Arg Lys Val Asn Glu Leu Arg Ala Phe Val Lys Met Cys
5 10 15

s Gln Asp Pro Ser Val Leu His Thr Glu Glu Met Arg Phe Leu Arg
20 25 30

u Trp Val Glu Ser Met Gly Gly Lys Val Pro Pro Ala Thr Gln Lys
35 40 45

a Lys Ser Glu Glu Asn Thr Lys Glu Glu Lys Pro Asp Ser Lys Lys
50 55 60

eolf-seql-S000001.txt

```
ıl Glu Glu Asp Leu Lys Ala Asp Glu Pro Ser Ser Glu Glu Ser Asp
;                      70                  75                  80

:u Glu Ile Asp Lys Glu Gly Val Ile Glu Pro Asp Thr Asp Ala Pro
               85                  90                  95

.n Glu Met Gly Asp Glu Asn Ala Glu Ile Thr Glu Glu Met Met Asp
           100                 105                 110

.n Ala Asn Asp Lys Lys Val Ala Ala Ile Glu Ala Leu Asn Asp Gly
       115                 120                 125

.u Leu Gln Lys Ala Ile Asp Leu Phe Thr Asp Ala Ile Lys Leu Asn
   130                 135                 140

'o Arg Leu Ala Ile Leu Tyr Ala Lys Arg Ala Ser Val Phe Val Lys
5                  150                 155                 160

·u Gln Lys Pro Asn Ala Ala Ile Arg Asp Cys Asp Arg Ala Ile Glu
               165                 170                 175

e Asn Pro Asp Ser Ala Gln Pro Tyr Lys Trp Arg Gly Lys Ala His
           180                 185                 190

g Leu Leu Gly His Trp Glu Glu Ala Ala His Asp Leu Ala Leu Ala
       195                 200                 205

s Lys Leu Asp Tyr Asp Glu Asp Ala Ser Ala Met Leu Lys Glu Val
   210                 215                 220

n Pro Arg Ala Gln Lys Ile Ala Glu His Arg Arg Lys Tyr Glu Arg
5                  230                 235                 240

s Arg Glu Glu Arg Glu Ile Lys Glu Arg Ile Glu Arg Val Lys Lys
               245                 250                 255

a Arg Glu Glu His Glu Arg Ala Gln Arg Glu Glu Glu Ala Arg Arg
           260                 265                 270

n Ser Gly Ala Gln Tyr Gly Ser Phe Pro Gly Gly Phe Pro Gly Gly
```

eolf-seql-S000001.txt

275 280 285

et Pro Gly Asn Phe Pro Gly Gly Met Pro Gly Met Gly Gly Gly Met
290 295 300

ro Gly Met Ala Gly Met Pro Gly Leu Asn Glu Ile Leu Ser Asp Pro
)5 310 315 320

Lu Val Leu Ala Ala Met Gln Asp Pro Glu Val Met Val Ala Phe Gln
325 330 335

sp Val Ala Gln Asn Pro Ala Asn Met Ser Lys Tyr Gln Ser Asn Pro
340 345 350

/s Val Met Asn Leu Ile Ser Lys Leu Ser Ala Lys Phe Gly Gly Gln
355 360 365

.a

<210> 170
<211> 440
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (21)..(21)
<223> Xaa can be any naturally occurring amino acid

<400> 170

et Glu Tyr Gln Ile Leu Lys Met Ser Leu Cys Leu Phe Ile Leu Leu
5 10 15

.e Leu Thr Pro Xaa Ile Leu Cys Ile Cys Pro Leu Gln Cys Ile Cys
20 25 30

.r Glu Arg His Arg His Val Asp Cys Ser Gly Arg Asn Leu Ser Thr
35 40 45

u Pro Ser Gly Leu Gln Glu Asn Ile Ile His Leu Asn Leu Ser Tyr
50 55 60

sn His Phe Thr Asp Leu His Asn Gln Leu Thr Gln Tyr Thr Asn Leu
5 70 75 80

rg Thr Leu Asp Ile Ser Asn Asn Arg Leu Glu Ser Leu Pro Ala His
85 90 95

eu Pro Arg Ser Leu Trp Asn Met Ser Ala Ala Asn Asn Asn Ile Lys
100 105 110

eu Leu Asp Lys Ser Asp Thr Ala Tyr Gln Trp Asn Leu Lys Tyr Leu
115 120 125

sp Val Ser Lys Asn Met Leu Glu Lys Val Val Leu Ile Lys Asn Thr
130 135 140

eu Arg Ser Leu Glu Val Leu Asn Leu Ser Ser Asn Lys Leu Trp Thr
15 150 155 160

al Pro Thr Asn Met Pro Ser Lys Leu His Ile Val Asp Leu Ser Asn
165 170 175

sn Ser Leu Thr Gln Ile Leu Pro Gly Thr Leu Ile Asn Leu Thr Asn
180 185 190

eu Thr His Leu Tyr Leu His Asn Asn Lys Phe Thr Phe Ile Pro Asp
195 200 205

n Ser Phe Asp Gln Leu Phe Gln Leu Gln Glu Ile Thr Leu Tyr Asn
210 215 220

n Arg Trp Ser Cys Asp His Lys Gln Asn Ile Thr Tyr Leu Leu Lys
5 230 235 240

p Met Met Glu Thr Lys Ala His Val Ile Gly Thr Pro Cys Ser Thr
245 250 255

n Ile Ser Ser Leu Lys Glu His Asn Met Tyr Pro Thr Pro Ser Gly
260 265 270

e Thr Ser Ser Leu Phe Thr Val Ser Gly Met Gln Thr Val Asp Thr
275 280 285

le Asn Ser Leu Ser Val Val Thr Gln Pro Lys Val Thr Lys Ile Pro
290 295 300

/s Gln Tyr Arg Thr Lys Glu Thr Thr Phe Gly Ala Thr Leu Ser Lys
)5 310 315 320

sp Thr Thr Phe Thr Ser Thr Asp Lys Ala Phe Val Pro Tyr Pro Glu
325 330 335

sp Thr Ser Thr Glu Thr Ile Asn Ser His Glu Ala Ala Ala Ala Thr
340 345 350

eu Thr Ile His Leu Gln Asp Gly Met Val Thr Asn Thr Ser Leu Thr
355 360 365

er Ser Thr Lys Ser Ser Pro Thr Pro Met Thr Leu Ser Ile Thr Ser
370 375 380

.y Met Pro Asn Asn Phe Ser Glu Met Pro Gln Gln Ser Thr Thr Leu
35 390 395 400

in Leu Trp Arg Glu Glu Thr Thr Thr Asn Val Lys Thr Pro Leu Pro
405 410 415

er Val Ala Asn Ala Trp Lys Val Asn Ala Ser Phe Leu Leu Leu Leu
420 425 430

n Val Val Val Met Leu Ala Val
435 440

10> 171
11> 241
12> PRT
13> Homo sapiens

00> 171

t Leu Ser Ser Thr Ala Met Tyr Ser Ala Pro Gly Arg Asp Leu Gly
5 10 15

t Glu Pro His Arg Ala Ala Gly Pro Leu Gln Leu Arg Phe Ser Pro
20 25 30

```
/r Val Phe Asn Gly Gly Thr Ile Leu Ala Ile Ala Gly Glu Asp Phe
       35                  40                  45

La Ile Val Ala Ser Asp Thr Arg Leu Ser Glu Gly Phe Ser Ile His
   50                  55                  60

ır Arg Asp Ser Pro Lys Cys Tyr Lys Leu Thr Asp Lys Thr Val Ile
;                  70                  75                  80

.y Cys Ser Gly Phe His Gly Asp Cys Leu Thr Leu Thr Lys Ile Ile
               85                  90                  95

.u Ala Arg Leu Lys Met Tyr Lys His Ser Asn Asn Lys Ala Met Thr
           100                 105                 110

ır Gly Ala Ile Ala Ala Met Leu Ser Thr Ile Leu Tyr Ser Arg Arg
       115                 120                 125

ıe Phe Pro Tyr Tyr Val Tyr Asn Ile Ile Gly Gly Leu Asp Glu Glu
   130                 135                 140

.y Lys Gly Ala Val Tyr Ser Phe Asp Pro Val Gly Ser Tyr Gln Arg
5                  150                 155                 160

p Ser Phe Lys Ala Gly Gly Ser Ala Ser Ala Met Leu Gln Pro Leu
               165                 170                 175

u Asp Asn Gln Val Gly Phe Lys Asn Met Gln Asn Val Glu His Val
           180                 185                 190

o Leu Ser Leu Asp Arg Ala Met Arg Leu Val Lys Asp Val Phe Ile
       195                 200                 205

r Ala Ala Glu Arg Asp Val Tyr Thr Gly Asp Ala Leu Arg Ile Cys
   210                 215                 220

e Val Thr Lys Glu Gly Ile Arg Glu Glu Thr Val Ser Leu Arg Lys
5                  230                 235                 240

p
```

:10> 172
:11> 83
:12> PRT
:13> Homo sapiens

:00> 172

:t Gln Asn Asp Ala Gly Glu Phe Val Asp Leu Tyr Val Pro Arg Lys
5 10 15

's Ser Ala Ser Asn Arg Ile Ile Gly Ala Lys Asp His Ala Ser Ile
20 25 30

n Met Asn Val Ala Glu Val Asp Lys Val Thr Gly Arg Phe Asn Gly
35 40 45

n Phe Lys Thr Tyr Ala Ile Cys Gly Ala Ile Arg Arg Met Gly Glu
50 55 60

r Asp Asp Ser Ile Leu Arg Leu Ala Lys Ala Asp Gly Ile Val Ser
70 75 80

s Asn Phe

10> 173
11> 660
12> PRT
13> Homo sapiens

00> 173

t Glu Ala Leu Met Ala Arg Gly Ala Leu Thr Gly Pro Leu Arg Ala
5 10 15

u Cys Leu Leu Gly Cys Leu Leu Ser His Ala Ala Ala Ala Pro Ser
20 25 30

ɔ Ile Ile Lys Phe Pro Gly Asp Val Ala Pro Lys Thr Asp Lys Glu
35 40 45

ı Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser
50 55 60

```
ys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe
5                  70                  75                  80

ne Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr
               85                  90                  95

et Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe
           100                 105                 110

ne Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile
       115                 120                 125

le Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe
   130                 135                 140

la Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser
15                 150                 155                 160

rg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp
               165                 170                 175

lu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala
           180                 185                 190

is Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser His Phe Asp
       195                 200                 205

p Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys
   210                 215                 220

r Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn
5                  230                 235                 240

y Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser Asp Gly Phe
               245                 250                 255

u Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly Lys Tyr Gly
           260                 265                 270

e Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn Ala Glu Gly
```

275 280 285

ln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser Tyr Asp Ser
290 295 300

ys Thr Thr Glu Gly Arg Thr Asp Gly Tyr Arg Trp Cys Gly Thr Thr
)5 310 315 320

.u Asp Tyr Asp Arg Asp Lys Lys Tyr Gly Phe Cys Pro Glu Thr Ala
325 330 335

et Ser Thr Val Gly Gly Asn Ser Glu Gly Ala Pro Cys Val Phe Pro
340 345 350

ne Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser Ala Gly Arg
355 360 365

er Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr Asp Asp Asp
370 375 380

'g Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val
:5 390 395 400

a Ala His Glu Phe Gly His Ala Met Gly Leu Glu His Ser Gln Asp
405 410 415

o Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys Asn Phe Arg
420 425 430

u Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr Gly Ala Ser
435 440 445

o Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu Gly Pro Val
450 455 460

r Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly Ile Ala Gln
5 470 475 480

e Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile Trp Arg Thr
485 490 495

ıl Thr Pro Arg Asp Lys Pro Met Gly Pro Leu Leu Val Ala Thr Phe
500 505 510

:p Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln
515 520 525

.u Glu Lys Ala Val Phe Phe Ala Gly Asn Glu Tyr Trp Ile Tyr Ser
530 535 540

.a Ser Thr Leu Glu Arg Gly Tyr Pro Lys Pro Leu Thr Ser Leu Gly
:5 550 555 560

:u Pro Pro Asp Val Gln Arg Val Asp Ala Ala Phe Asn Trp Ser Lys
565 570 575

:n Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp Arg Tyr Asn
580 585 590

.u Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp
595 600 605

a Trp Asn Ala Ile Pro Asp Asn Leu Asp Ala Val Val Asp Leu Gln
610 615 620

y Gly Gly His Ser Tyr Phe Phe Lys Gly Ala Tyr Tyr Leu Lys Leu
5 630 635 640

u Asn Gln Ser Leu Lys Ser Val Lys Phe Gly Ser Ile Lys Ser Asp
645 650 655

p Leu Gly Cys
660

10> 174
11> 245
12> PRT
13> Homo sapiens

00> 174

t Asp Lys Asn Glu Leu Val Gln Lys Ala Lys Leu Ala Glu Gln Ala
5 10 15

eolf-seql-S000001.txt

```
.u Arg Tyr Asp Asp Met Ala Ala Cys Met Lys Ser Val Thr Glu Gln
           20                  25                  30

.y Ala Glu Leu Ser Asn Glu Glu Arg Asn Leu Leu Ser Val Ala Tyr
       35                  40                  45

's Asn Val Val Gly Ala Arg Arg Ser Ser Trp Arg Val Val Ser Ser
   50                  55                  60

.e Glu Gln Lys Thr Glu Gly Ala Glu Lys Lys Gln Gln Met Ala Arg
;                  70                  75                  80

.u Tyr Arg Glu Lys Ile Glu Thr Glu Leu Arg Asp Ile Cys Asn Asp
               85                  90                  95

:l Leu Ser Leu Leu Glu Lys Phe Leu Ile Pro Asn Ala Ser Gln Ala
           100                 105                 110

.u Ser Lys Val Phe Tyr Leu Lys Met Lys Gly Asp Tyr Tyr Arg Tyr
       115                 120                 125

:u Ala Glu Val Ala Ala Gly Asp Asp Lys Lys Gly Ile Val Asp Gln
   130                 135                 140

r Gln Gln Ala Tyr Gln Glu Ala Phe Glu Ile Ser Lys Lys Glu Met
5                  150                 155                 160

n Pro Thr His Pro Ile Arg Leu Gly Leu Ala Leu Asn Phe Ser Val
               165                 170                 175

e Tyr Tyr Glu Ile Leu Asn Ser Pro Glu Lys Ala Cys Ser Leu Ala
           180                 185                 190

s Thr Ala Phe Asp Glu Ala Ile Ala Glu Leu Asp Thr Leu Ser Glu
       195                 200                 205

u Ser Tyr Lys Asp Ser Thr Leu Ile Met Gln Leu Leu Arg Asp Asn
   210                 215                 220

u Thr Leu Trp Thr Ser Asp Thr Gln Gly Asp Glu Ala Glu Ala Gly
5                  230                 235                 240
```

.u Gly Gly Glu Asn
245

:10> 175
:11> 173
:12> PRT
:13> Homo sapiens

!00> 175

:t Ser Thr Met Gly Asn Glu Ala Ser Tyr Pro Ala Glu Met Cys Ser
5 10 15

.s Phe Asp Asn Asp Glu Ile Lys Arg Leu Gly Arg Arg Phe Lys Lys
20 25 30

:u Asp Leu Asp Lys Ser Gly Ser Leu Ser Val Glu Glu Phe Met Ser
35 40 45

:u Pro Glu Leu Arg His Asn Pro Leu Val Arg Arg Val Ile Asp Val
50 55 60

.e Asp Thr Asp Gly Asp Gly Glu Val Asp Phe Lys Glu Phe Ile Leu
70 75 80

y Thr Ser Gln Phe Ser Val Lys Gly Asp Glu Glu Gln Lys Leu Arg
85 90 95

e Ala Phe Ser Ile Tyr Asp Met Asp Lys Asp Gly Tyr Ile Ser Asn
100 105 110

y Glu Leu Phe Gln Val Leu Lys Met Met Val Gly Asn Asn Leu Thr
115 120 125

p Trp Gln Leu Gln Gln Leu Val Asp Lys Thr Ile Ile Ile Leu Asp
130 135 140

s Asp Gly Asp Gly Lys Ile Ser Phe Glu Glu Phe Ser Ala Val Val
5 150 155 160

g Asp Leu Glu Ile His Lys Lys Leu Val Leu Ile Val
165 170

:10> 176
:11> 907
:12> PRT
:13> Homo sapiens

100> 176

:t Thr Ala Val His Ala Gly Asn Ile Asn Phe Lys Trp Asp Pro Lys
5 10 15

:r Leu Glu Ile Arg Thr Leu Ala Val Glu Arg Leu Leu Glu Pro Leu
20 25 30

ıl Thr Gln Val Thr Thr Leu Val Asn Thr Asn Ser Lys Gly Pro Ser
35 40 45

:n Lys Lys Arg Gly Arg Ser Lys Lys Ala His Val Leu Ala Ala Ser
50 55 60

.l Glu Gln Ala Thr Glu Asn Phe Leu Glu Lys Gly Asp Lys Ile Ala
70 75 80

's Glu Ser Gln Phe Leu Lys Glu Glu Leu Val Val Ala Val Glu Asp
85 90 95

l Arg Lys Gln Gly Asp Leu Met Lys Ala Ala Ala Gly Glu Phe Ala
100 105 110

p Asp Pro Cys Ser Ser Val Lys Arg Gly Asn Met Val Arg Ala Ala
115 120 125

g Ala Leu Leu Ser Ala Val Thr Arg Leu Leu Ile Leu Ala Asp Met
130 135 140

a Asp Val Tyr Lys Leu Leu Val Gln Leu Lys Val Val Glu Asp Gly
5 150 155 160

e Leu Lys Leu Arg Asn Ala Gly Asn Glu Gln Asp Leu Gly Asn Gln
165 170 175

r Lys Ala Leu Lys Pro Glu Val Asp Lys Leu Asn Ile Met Ala Ala
180 185 190

ys Arg Gln Gln Glu Leu Lys Asp Val Gly His Arg Asp Gln Met Ala
195 200 205

la Ala Arg Gly Ile Leu Gln Ser Asn Val Pro Ile Leu Tyr Thr Ala
210 215 220

er Gln Ala Cys Leu Gln His Pro Asp Val Ala Ala Tyr Lys Ala Asn
25 230 235 240

rg Asp Leu Ile Tyr Lys Gln Leu Gln Gln Ala Val Thr Gly Ile Ser
245 250 255

sn Ala Ala Gln Ala Thr Ala Ser Asp Asp Ala Ser Gln His Gln Gly
260 265 270

y Gly Gly Gly Glu Leu Ala Tyr Ala Leu Asn Asn Phe Asp Lys Gln
275 280 285

e Ile Val Asp Pro Leu Ser Phe Ser Glu Glu Arg Phe Arg Pro Ser
290 295 300

eu Glu Glu Arg Leu Glu Ser Ile Ile Ser Gly Ala Ala Leu Met Ala
05 310 315 320

sp Ser Ser Cys Thr Arg Asp Asp Arg Arg Glu Arg Ile Val Ala Glu
325 330 335

's Asn Ala Val Arg Gln Ala Cys Arg Thr Cys Val Ser Glu Tyr Met
340 345 350

y Asn Ala Gly Arg Lys Glu Arg Ser Asp Ala Leu Asn Ser Ala Ile
355 360 365

p Lys Met Thr Lys Lys Thr Arg Asp Leu Arg Arg Gln Leu Arg Lys
370 375 380

a Val Met Asp His Val Ser Asp Ser Phe Leu Glu Thr Asn Val Pro
5 390 395 400

u Leu Val Leu Ile Glu Ala Ala Lys Asn Gly Asn Glu Lys Glu Val
405 410 415

```
ys Glu Tyr Ala Gln Val Phe Arg Glu His Ala Asn Lys Leu Ile Glu
           420                 425                 430

al Ala Asn Leu Ala Cys Ser Ile Ser Asn Asn Glu Glu Gly Val Lys
       435                 440                 445

eu Val Arg Met Ser Ala Ser Gln Leu Glu Ala Gly Cys Pro Gln Val
   450                 455                 460

le Asn Ala Ala Thr Trp Ala Leu Ala Pro Lys Pro Gln Ser Lys Leu
55                  470                 475                 480

.a Gln Glu Asn Met Asp Leu Phe Lys Glu Gln Trp Glu Lys Gln Val
               485                 490                 495

:g Val Leu Thr Asp Ala Val Asp Asp Ile Thr Ser Ile Asp Asp Phe
           500                 505                 510

eu Ala Val Ser Glu Asn His Ile Leu Glu Asp Val Asn Lys Cys Val
       515                 520                 525

.e Ala Leu Gln Glu Lys Asp Val Asp Gly Leu Asp Arg Thr Ala Gly
   530                 535                 540

.a Ile Arg Gly Arg Ala Ala Arg Val Ile His Val Val Thr Ser Glu
5                   550                 555                 560

:t Asp Asn Tyr Glu Pro Gly Val Tyr Thr Glu Lys Val Leu Glu Ala
               565                 570                 575

.r Lys Leu Leu Ser Asn Thr Val Met Pro Arg Phe Thr Glu Gln Val
           580                 585                 590

u Ala Ala Val Glu Ala Leu Ser Ser Asp Pro Ala Gln Pro Met Asp
       595                 600                 605

u Asn Glu Phe Ile Asp Ala Ser Arg Leu Val Tyr Asp Gly Ile Arg
   610                 615                 620

p Ile Arg Lys Ala Val Leu Met Ile Arg Thr Pro Glu Glu Leu Asp
```

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5 630 635 640

p Ser Asp Phe Glu Thr Glu Asp Phe Asp Val Arg Ser Glu Thr Ser
645 650 655

l Gln Thr Glu Asp Asp Gln Leu Ile Ala Gly Gln Ser Ala Arg Ala
660 665 670

e Met Ala Gln Leu Pro Gln Glu Gln Lys Ala Lys Ile Arg Glu Gln
675 680 685

l Ala Ser Phe Gln Glu Glu Lys Ser Lys Leu Asp Ala Glu Val Ser
690 695 700

s Trp Asp Asp Ser Gly Asn Asp Ile Ile Val Leu Ala Lys Gln Met
5 710 715 720

s Met Ile Met Met Glu Met Thr Asp Phe Thr Arg Gly Lys Gly Pro
725 730 735

u Lys Asn Thr Ser Asp Val Ile Ser Ala Ala Lys Lys Ile Ala Glu
740 745 750

a Gly Ser Arg Met Asp Lys Leu Gly Arg Thr Ile Arg Asp His Cys
755 760 765

ɔ Asp Ser Ala Cys Lys Gln Asp Leu Leu Ala Tyr Leu Gln Arg Ile
770 775 780

a Leu Tyr Cys His Gln Leu Asn Ile Cys Ser Lys Val Lys Ala Glu
5 790 795 800

l Gln Asn Leu Gly Gly Glu Leu Val Val Ser Gly Val Asp Ser Ala
805 810 815

: Ser Leu Ile Gln Ala Ala Lys Asn Leu Met Asn Ala Val Val Gln
820 825 830

: Val Lys Ala Ser Tyr Val Ala Ser Thr Lys Tyr Gln Lys Ser Gln
835 840 845

ly Met Ala Ser Leu Asn Leu Pro Ala Val Ser Met Lys Met Lys Ala
850 855 860

ro Glu Lys Lys Pro Leu Val Lys Arg Glu Lys Gln Asp Glu Thr Gln
55 870 875 880

ır Lys Ile Lys Arg Ala Ser Gln Lys Lys His Val Asn Pro Val Gln
885 890 895

.a Leu Ser Glu Phe Lys Ala Met Asp Ser Ile
900 905

:10> 177
:11> 176
:12> PRT
:13> Homo sapiens

!00> 177

:t Thr Met Cys Ser Gly Ala Arg Leu Ala Leu Leu Val Tyr Gly Ile
5 10 15

.e Met His Ser Ser Val Tyr Ser Ser Pro Ala Ala Ala Gly Leu Arg
20 25 30

ıe Pro Gly Ile Arg Pro Glu Glu Glu Ala Tyr Gly Glu Asp Gly Asn
35 40 45

'o Leu Pro Asp Phe Gly Gly Ser Glu Pro Pro Gly Ala Gly Ser Pro
50 55 60

a Ser Ala Pro Arg Ala Ala Ala Ala Trp Tyr Arg Pro Ala Gly Arg
70 75 80

g Asp Val Ala His Gly Ile Leu Asn Glu Ala Tyr Arg Lys Val Leu
85 90 95

p Gln Leu Ser Ala Gly Lys His Leu Gln Ser Leu Val Ala Arg Gly
100 105 110

l Gly Gly Ser Leu Gly Gly Gly Ala Gly Asp Asp Ala Glu Pro Leu
115 120 125

eolf-seql-S000001.txt

ɘr Lys Arg His Ser Asp Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr
130 135 140

:g Lys Gln Met Ala Val Lys Lys Tyr Leu Ala Ala Val Leu Gly Lys
ı5 150 155 160

:g Tyr Lys Gln Arg Val Lys Asn Lys Gly Arg Arg Ile Ala Tyr Leu
165 170 175

:10> 178
:11> 298
:12> PRT
:13> Homo sapiens

ı00> 178

:t Ser Leu Tyr Pro Ser Leu Glu Asp Leu Lys Val Asp Lys Val Ile
5 10 15

.n Ala Gln Thr Ala Phe Ser Ala Asn Pro Ala Asn Pro Ala Ile Leu
20 25 30

:r Glu Ala Ser Ala Pro Ile Pro His Asp Gly Asn Leu Tyr Pro Arg
35 40 45

:u Tyr Pro Glu Leu Ser Gln Tyr Met Gly Leu Ser Leu Asn Glu Glu
50 55 60

u Ile Arg Ala Ser Val Ala Val Val Ser Gly Ala Pro Leu Gln Gly
70 75 80

n Leu Val Ala Arg Pro Ser Ser Ile Asn Tyr Met Val Ala Pro Val
85 90 95

r Gly Asn Asp Val Gly Ile Arg Arg Ala Glu Ile Lys Gln Gly Ile
100 105 110

g Glu Val Ile Leu Cys Lys Asp Gln Asp Gly Lys Ile Gly Leu Arg
115 120 125

u Lys Ser Ile Asp Asn Gly Ile Phe Val Gln Leu Val Gln Ala Asn
130 135 140

```
er Pro Ala Ser Leu Val Gly Leu Arg Phe Gly Asp Gln Val Leu Gln
15                 150                 155                 160

.e Asn Gly Glu Asn Cys Ala Gly Trp Ser Ser Asp Lys Ala His Lys
               165                 170                 175

ıl Leu Lys Gln Ala Phe Gly Glu Lys Ile Thr Met Thr Ile Arg Asp
            180                 185                 190

:g Pro Phe Glu Arg Thr Ile Thr Met His Lys Asp Ser Thr Gly His
        195                 200                 205

ıl Gly Phe Ile Phe Lys Asn Gly Lys Ile Thr Ser Ile Val Lys Asp
    210                 215                 220

:r Ser Ala Ala Arg Asn Gly Leu Leu Thr Glu His Asn Ile Cys Glu
:5                 230                 235                 240

.e Asn Gly Gln Asn Val Ile Gly Leu Lys Asp Ser Gln Ile Ala Asp
               245                 250                 255

e Leu Ser Thr Ser Gly Thr Val Val Thr Ile Thr Ile Met Pro Ala
            260                 265                 270

e Ile Phe Glu His Ile Ile Lys Arg Met Ala Pro Ser Ile Met Lys
        275                 280                 285

r Leu Met Asp His Thr Ile Pro Glu Val
    290                 295


10>  179
11>  1621
12>  PRT
13>  Homo sapiens

00>  179

t Ala Lys Ser Gly Gly Cys Gly Ala Gly Ala Gly Val Gly Gly Gly
               5                   10                  15

n Gly Ala Leu Thr Trp Val Asn Asn Ala Ala Lys Lys Glu Glu Ser
            20                  25                  30
```

```
.u Thr Ala Asn Lys Asn Asp Ser Ser Lys Lys Leu Ser Val Glu Arg
       35                  40                  45

ıl Tyr Gln Lys Lys Thr Gln Leu Glu His Ile Leu Leu Arg Pro Asp
   50                  55                  60

ır Tyr Ile Gly Ser Val Glu Pro Leu Thr Gln Phe Met Trp Val Tyr
;                  70                  75                  80

ıp Glu Asp Val Gly Met Asn Cys Arg Glu Val Thr Phe Val Pro Gly
               85                  90                  95

ːu Tyr Lys Ile Phe Asp Glu Ile Leu Val Asn Ala Ala Asp Asn Lys
           100                 105                 110

n Arg Asp Lys Asn Met Thr Cys Ile Lys Val Ser Ile Asp Pro Glu
       115                 120                 125

r Asn Ile Ile Ser Ile Trp Asn Asn Gly Lys Gly Ile Pro Val Val
   130                 135                 140

u His Lys Val Glu Lys Val Tyr Val Pro Ala Leu Ile Phe Gly Gln
5                  150                 155                 160

u Leu Thr Ser Ser Asn Tyr Asp Asp Asp Glu Lys Lys Val Thr Gly
               165                 170                 175

y Arg Asn Gly Tyr Gly Ala Lys Leu Cys Asn Ile Phe Ser Thr Lys
           180                 185                 190

e Thr Val Glu Thr Ala Cys Lys Glu Tyr Lys His Ser Phe Lys Gln
       195                 200                 205

r Trp Met Asn Asn Met Met Lys Thr Ser Glu Ala Lys Ile Lys His
   210                 215                 220

e Asp Gly Glu Asp Tyr Thr Cys Ile Thr Phe Gln Pro Asp Leu Ser
5                  230                 235                 240

s Phe Lys Met Glu Lys Leu Asp Lys Asp Ile Val Ala Leu Met Thr
               245                 250                 255
```

```
:g Arg Ala Tyr Asp Leu Ala Gly Ser Cys Arg Gly Val Lys Val Met
           260                 265                 270

ıe Asn Gly Lys Lys Leu Pro Val Asn Gly Phe Arg Ser Tyr Val Asp
       275                 280                 285

ɜu Tyr Val Lys Asp Lys Leu Asp Glu Thr Gly Val Ala Leu Lys Val
   290                 295                 300

.e His Glu Leu Ala Asn Glu Arg Trp Asp Val Cys Leu Thr Leu Ser
)5                 310                 315                 320

.u Lys Gly Phe Gln Gln Ile Ser Phe Val Asn Ser Ile Ala Thr Thr
               325                 330                 335

's Gly Gly Arg His Val Asp Tyr Val Val Asp Gln Val Val Gly Lys
           340                 345                 350

ɜu Ile Glu Val Val Lys Lys Lys Asn Lys Ala Gly Val Ser Val Lys
       355                 360                 365

:o Phe Gln Val Lys Asn His Ile Trp Val Phe Ile Asn Cys Leu Ile
   370                 375                 380

.u Asn Pro Thr Phe Asp Ser Gln Thr Lys Glu Asn Met Thr Leu Gln
:5                 390                 395                 400

'o Lys Ser Phe Gly Ser Lys Cys Gln Leu Ser Glu Lys Phe Phe Lys
               405                 410                 415

a Ala Ser Asn Cys Gly Ile Val Glu Ser Ile Leu Asn Trp Val Lys
           420                 425                 430

e Lys Ala Gln Thr Gln Leu Asn Lys Lys Cys Ser Ser Val Lys Tyr
       435                 440                 445

r Lys Ile Lys Gly Ile Pro Lys Leu Asp Asp Ala Asn Asp Ala Gly
   450                 455                 460

y Lys His Ser Leu Glu Cys Thr Leu Ile Leu Thr Glu Gly Asp Ser
5                  470                 475                 480
```

```
.a Lys Ser Leu Ala Val Ser Gly Leu Gly Val Ile Gly Arg Asp Arg
                485                     490                     495

'r Gly Val Phe Pro Leu Arg Gly Lys Ile Leu Asn Val Arg Glu Ala
            500                     505                     510

:r His Lys Gln Ile Met Glu Asn Ala Glu Ile Asn Asn Ile Ile Lys
        515                     520                     525

.e Val Gly Leu Gln Tyr Lys Lys Ser Tyr Asp Asp Ala Glu Ser Leu
    530                     535                     540

's Thr Leu Arg Tyr Gly Lys Ile Met Ile Met Thr Asp Gln Asp Gln
.5                      550                     555                     560

.p Gly Ser His Ile Lys Gly Leu Leu Ile Asn Phe Ile His His Asn
                565                     570                     575

'p Pro Ser Leu Leu Lys His Gly Phe Leu Glu Glu Phe Ile Thr Pro
            580                     585                     590

e Val Lys Ala Ser Lys Asn Lys Gln Glu Leu Ser Phe Tyr Ser Ile
        595                     600                     605

o Glu Phe Asp Glu Trp Lys Lys His Ile Glu Asn Gln Lys Ala Trp
    610                     615                     620

s Ile Lys Tyr Tyr Lys Gly Leu Gly Thr Ser Thr Ala Lys Glu Ala
5                       630                     635                     640

s Glu Tyr Phe Ala Asp Met Glu Arg His Arg Ile Leu Phe Arg Tyr
                645                     650                     655

a Gly Pro Glu Asp Asp Ala Ala Ile Thr Leu Ala Phe Ser Lys Lys
            660                     665                     670

s Ile Asp Asp Arg Lys Glu Trp Leu Thr Asn Phe Met Glu Asp Arg
        675                     680                     685

g Gln Arg Arg Leu His Gly Leu Pro Glu Gln Phe Leu Tyr Gly Thr
```

690 695 700

la Thr Lys His Leu Thr Tyr Asn Asp Phe Ile Asn Lys Glu Leu Ile
)5 710 715 720

eu Phe Ser Asn Ser Asp Asn Glu Arg Ser Ile Pro Ser Leu Val Asp
725 730 735

ly Phe Lys Pro Gly Gln Arg Lys Val Leu Phe Thr Cys Phe Lys Arg
740 745 750

sn Asp Lys Arg Glu Val Lys Val Ala Gln Leu Ala Gly Ser Val Ala
755 760 765

lu Met Ser Ala Tyr His His Gly Glu Gln Ala Leu Met Met Thr Ile
770 775 780

al Asn Leu Ala Gln Asn Phe Val Gly Ser Asn Asn Ile Asn Leu Leu
35 790 795 800

n Pro Ile Gly Gln Phe Gly Thr Arg Leu His Gly Gly Lys Asp Ala
805 810 815

a Ser Pro Arg Tyr Ile Phe Thr Met Leu Ser Thr Leu Ala Arg Leu
820 825 830

u Phe Pro Ala Val Asp Asp Asn Leu Leu Lys Phe Leu Tyr Asp Asp
835 840 845

n Gln Arg Val Glu Pro Glu Trp Tyr Ile Pro Ile Ile Pro Met Val
850 855 860

u Ile Asn Gly Ala Glu Gly Ile Gly Thr Gly Trp Ala Cys Lys Leu
5 870 875 880

o Asn Tyr Asp Ala Arg Glu Ile Val Asn Asn Val Arg Arg Met Leu
885 890 895

p Gly Leu Asp Pro His Pro Met Leu Pro Asn Tyr Lys Asn Phe Lys
900 905 910

ly Thr Ile Gln Glu Leu Gly Gln Asn Gln Tyr Ala Val Ser Gly Glu
915 920 925

le Phe Val Val Asp Arg Asn Thr Val Glu Ile Thr Glu Leu Pro Val
930 935 940

:g Thr Trp Thr Gln Val Tyr Lys Glu Gln Val Leu Glu Pro Met Leu
15 950 955 960

;n Gly Thr Asp Lys Thr Pro Ala Leu Ile Ser Asp Tyr Lys Glu Tyr
965 970 975

.s Thr Asp Thr Thr Val Lys Phe Val Val Lys Met Thr Glu Glu Lys
980 985 990

:u Ala Gln Ala Glu Ala Ala Gly Leu His Lys Val Phe Lys Leu Gln
995 1000 1005

ır Thr Leu Thr Cys Asn Ser Met Val Leu Phe Asp His Met Gly
1010 1015 1020

's Leu Lys Lys Tyr Glu Thr Val Gln Asp Ile Leu Lys Glu Phe
1025 1030 1035

ıe Asp Leu Arg Leu Ser Tyr Tyr Gly Leu Arg Lys Glu Trp Leu
1040 1045 1050

.l Gly Met Leu Gly Ala Glu Ser Thr Lys Leu Asn Asn Gln Ala
1055 1060 1065

g Phe Ile Leu Glu Lys Ile Gln Gly Lys Ile Thr Ile Glu Asn
1070 1075 1080

g Ser Lys Lys Asp Leu Ile Gln Met Leu Val Gln Arg Gly Tyr
1085 1090 1095

u Ser Asp Pro Val Lys Ala Trp Lys Glu Ala Gln Glu Lys Ala
1100 1105 1110

a Glu Glu Asp Glu Thr Gln Asn Gln His Asp Asp Ser Ser Ser
1115 1120 1125

sp Ser Gly Thr Pro Ser Gly Pro Asp Phe Asn Tyr Ile Leu Asn
1130 1135 1140

et Ser Leu Trp Ser Leu Thr Lys Glu Lys Val Glu Glu Leu Ile
1145 1150 1155

's Gln Arg Asp Ala Lys Gly Arg Glu Val Asn Asp Leu Lys Arg
1160 1165 1170

's Ser Pro Ser Asp Leu Trp Lys Glu Asp Leu Ala Ala Phe Val
1175 1180 1185

.u Glu Leu Asp Lys Val Glu Ser Gln Glu Arg Glu Asp Val Leu
1190 1195 1200

.a Gly Met Ser Gly Lys Ala Ile Lys Gly Lys Val Gly Lys Pro
1205 1210 1215

's Val Lys Lys Leu Gln Leu Glu Glu Thr Met Pro Ser Pro Tyr
1220 1225 1230

.y Arg Arg Ile Ile Pro Glu Ile Thr Ala Met Lys Ala Asp Ala
1235 1240 1245

r Lys Lys Leu Leu Lys Lys Lys Lys Gly Asp Leu Asp Thr Ala
1250 1255 1260

a Val Lys Val Glu Phe Asp Glu Glu Phe Ser Gly Ala Pro Val
1265 1270 1275

u Gly Ala Gly Glu Glu Ala Leu Thr Pro Ser Val Pro Ile Asn
1280 1285 1290

s Gly Pro Lys Pro Lys Arg Glu Lys Lys Glu Pro Gly Thr Arg
1295 1300 1305

l Arg Lys Thr Pro Thr Ser Ser Gly Lys Pro Ser Ala Lys Lys
1310 1315 1320

l Lys Lys Arg Asn Pro Trp Ser Asp Asp Glu Ser Lys Ser Glu
1325 1330 1335

er Asp Leu Glu Glu Thr Glu Pro Val Val Ile Pro Arg Asp Ser
1340 1345 1350

eu Leu Arg Arg Ala Ala Ala Glu Arg Pro Lys Tyr Thr Phe Asp
1355 1360 1365

ne Ser Glu Glu Glu Asp Asp Asp Ala Asp Asp Asp Asp Asp Asp
1370 1375 1380

sn Asn Asp Leu Glu Glu Leu Lys Val Lys Ala Ser Pro Ile Thr
1385 1390 1395

sn Asp Gly Glu Asp Glu Phe Val Pro Ser Asp Gly Leu Asp Lys
1400 1405 1410

p Glu Tyr Thr Phe Ser Pro Gly Lys Ser Lys Ala Thr Pro Glu
1415 1420 1425

's Ser Leu His Asp Lys Lys Ser Gln Asp Phe Gly Asn Leu Phe
1430 1435 1440

r Phe Pro Ser Tyr Ser Gln Lys Ser Glu Asp Asp Ser Ala Lys
1445 1450 1455

e Asp Ser Asn Glu Glu Asp Ser Ala Ser Val Phe Ser Pro Ser
1460 1465 1470

e Gly Leu Lys Gln Thr Asp Lys Val Pro Ser Lys Thr Val Ala
1475 1480 1485

a Lys Lys Gly Lys Pro Ser Ser Asp Thr Val Pro Lys Pro Lys
1490 1495 1500

g Ala Pro Lys Gln Lys Lys Val Val Glu Ala Val Asn Ser Asp
1505 1510 1515

r Asp Ser Glu Phe Gly Ile Pro Lys Lys Thr Thr Thr Pro Lys
1520 1525 1530

y Lys Gly Arg Gly Ala Lys Lys Arg Lys Ala Ser Gly Ser Glu

1535 1540 1545

sn Glu Gly Asp Tyr Asn Pro Gly Arg Lys Thr Ser Lys Thr Thr
1550 1555 1560

er Lys Lys Pro Lys Lys Thr Ser Phe Asp Gln Asp Ser Asp Val
1565 1570 1575

sp Ile Phe Pro Ser Asp Phe Pro Thr Glu Pro Pro Ser Leu Pro
1580 1585 1590

rg Thr Gly Arg Ala Arg Lys Glu Val Lys Tyr Phe Ala Glu Ser
1595 1600 1605

sp Glu Glu Glu Asp Asp Val Asp Phe Ala Met Phe Asn
1610 1615 1620

:10> 180
:11> 228
:12> PRT
:13> Homo sapiens

:00> 180

et Leu Ser Arg Cys Arg Ser Gly Leu Leu His Val Leu Gly Leu Ser
5 10 15

le Leu Leu Gln Thr Arg Arg Pro Ile Leu Leu Cys Ser Pro Arg Leu
20 25 30

et Lys Pro Leu Val Val Phe Val Leu Gly Gly Pro Gly Ala Gly Lys
35 40 45

y Thr Gln Cys Ala Arg Ile Val Glu Lys Tyr Gly Tyr Thr His Leu
50 55 60

r Ala Gly Glu Leu Leu Arg Asp Glu Arg Lys Asn Pro Asp Ser Gln
70 75 80

r Gly Glu Leu Ile Glu Lys Tyr Ile Lys Glu Gly Lys Ile Val Pro
85 90 95

l Glu Ile Thr Ile Ser Leu Leu Lys Arg Glu Met Asp Gln Thr Met

100 105 110

.a Ala Asn Ala Gln Lys Asn Lys Phe Leu Ile Asp Gly Phe Pro Arg
115 120 125

:n Gln Asp Asn Leu Gln Gly Trp Asn Lys Thr Met Asp Gly Lys Ala
130 135 140

.p Val Ser Phe Val Leu Phe Phe Asp Cys Asn Asn Glu Ile Cys Ile
5 150 155 160

u Arg Cys Leu Glu Arg Gly Lys Ser Ser Gly Arg Ser Asp Asp Asn
165 170 175

g Glu Ser Leu Glu Lys Arg Ile Gln Thr Tyr Leu Gln Ser Thr Lys
180 185 190

o Ile Ile Asp Leu Tyr Glu Glu Met Gly Lys Val Lys Lys Ile Asp
195 200 205

a Ser Lys Ser Val Asp Glu Val Phe Asp Glu Val Val Gln Ile Phe
210 215 220

p Lys Glu Gly
5

10> 181
11> 268
12> PRT
13> Homo sapiens

00> 181

t Val Leu Glu Ser Thr Met Val Cys Val Asp Asn Ser Glu Tyr Met
5 10 15

g Asn Gly Asp Phe Leu Pro Thr Arg Leu Gln Ala Gln Gln Asp Ala
20 25 30

l Asn Ile Val Cys His Ser Lys Thr Arg Ser Asn Pro Glu Asn Asn
35 40 45

l Gly Leu Ile Thr Leu Ala Asn Asp Cys Glu Val Leu Thr Thr Leu

50 55 60

ır Pro Asp Thr Gly Arg Ile Leu Ser Lys Leu His Thr Val Gln Pro
5 70 75 80

ys Gly Lys Ile Thr Phe Cys Thr Gly Ile Arg Val Ala His Leu Ala
85 90 95

eu Lys His Arg Gln Gly Lys Asn His Lys Met Arg Ile Ile Ala Phe
100 105 110

al Gly Ser Pro Val Glu Asp Asn Glu Lys Asp Leu Val Lys Leu Ala
115 120 125

's Arg Leu Lys Lys Glu Lys Val Asn Val Asp Ile Ile Asn Phe Gly
130 135 140

.u Glu Glu Val Asn Thr Glu Lys Leu Thr Ala Phe Val Asn Thr Leu
5 150 155 160

n Gly Lys Asp Gly Thr Gly Ser His Leu Val Thr Val Pro Pro Gly
165 170 175

o Ser Leu Ala Asp Ala Leu Ile Ser Ser Pro Ile Leu Ala Gly Glu
180 185 190

y Gly Ala Met Leu Gly Leu Gly Ala Ser Asp Phe Glu Phe Gly Val
195 200 205

p Pro Ser Ala Asp Pro Glu Leu Ala Leu Ala Leu Arg Val Ser Met
210 215 220

u Glu Gln Arg Gln Arg Gln Glu Glu Glu Ala Arg Arg Ala Ala Ala
5 230 235 240

a Ser Ala Ala Glu Ala Gly Ile Ala Thr Thr Gly Thr Glu Gly Glu
245 250 255

g Gly Gly Ile Arg Ser Pro Gly Thr Ala Gly Cys
260 265

eolf-seql-S000001.txt

:10> 182
:11> 162
:12> PRT
:13> Homo sapiens

:00> 182

:t Lys Glu Thr Ile Met Asn Gln Glu Lys Leu Ala Lys Leu Gln Ala
5 10 15

.n Val Arg Ile Gly Gly Lys Gly Thr Ala Arg Arg Lys Lys Lys Val
20 25 30

.l His Arg Thr Ala Thr Ala Asp Asp Lys Lys Leu Gln Phe Ser Leu
35 40 45

's Lys Leu Gly Val Asn Asn Ile Ser Gly Ile Glu Glu Val Asn Met
50 55 60

.e Thr Asn Gln Gly Thr Val Ile His Phe Asn Asn Pro Lys Val Gln
70 75 80

a Ser Leu Ala Ala Asn Thr Phe Thr Ile Thr Gly His Ala Glu Thr
85 90 95

s Gln Leu Thr Glu Met Leu Pro Ser Ile Leu Asn Gln Leu Gly Ala
100 105 110

p Ser Leu Thr Ser Leu Arg Arg Leu Ala Glu Ala Leu Pro Lys Gln
115 120 125

r Val Asp Gly Lys Ala Pro Leu Ala Thr Gly Glu Asp Asp Asp Asp
130 135 140

u Val Pro Asp Leu Val Glu Asn Phe Asp Glu Ala Ser Lys Asn Glu
5 150 155 160

a Asn

10> 183
11> 193
12> PRT
13> Homo sapiens

eolf-seql-S000001.txt

ı00> 183

ɜt Ala Ala Ile Arg Lys Lys Leu Val Ile Val Gly Asp Gly Ala Cys
5 10 15

.y Lys Thr Cys Leu Leu Ile Val Phe Ser Lys Asp Gln Phe Pro Glu
20 25 30

ıl Tyr Val Pro Thr Val Phe Glu Asn Tyr Val Ala Asp Ile Glu Val
35 40 45

ıp Gly Lys Gln Val Glu Leu Ala Leu Trp Asp Thr Ala Gly Gln Glu
50 55 60

ıp Tyr Asp Arg Leu Arg Pro Leu Ser Tyr Pro Asp Thr Asp Val Ile
70 75 80

ıu Met Cys Phe Ser Ile Asp Ser Pro Asp Ser Leu Glu Asn Ile Pro
85 90 95

u Lys Trp Thr Pro Glu Val Lys His Phe Cys Pro Asn Val Pro Ile
100 105 110

e Leu Val Gly Asn Lys Lys Asp Leu Arg Asn Asp Glu His Thr Arg
115 120 125

g Glu Leu Ala Lys Met Lys Gln Glu Pro Val Lys Pro Glu Glu Gly
130 135 140

g Asp Met Ala Asn Arg Ile Gly Ala Phe Gly Tyr Met Glu Cys Ser
5 150 155 160

a Lys Thr Lys Asp Gly Val Arg Glu Val Phe Glu Met Ala Thr Arg
165 170 175

a Ala Leu Gln Ala Arg Arg Gly Lys Lys Lys Ser Gly Cys Leu Val
180 185 190

u

eolf-seql-S000001.txt

:10> 184
:11> 334
:12> PRT
:13> Homo sapiens

00> 184

:t Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Glu Glu Glu
5 10 15

a Thr Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val
20 25 30

y Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu
35 40 45

u Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met
50 55 60

p Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala
70 75 80

p Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
85 90 95

a Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln
100 105 110

g Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr
115 120 125

r Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu
130 135 140

r Tyr Val Thr Trp Lys Leu Ser Gly Leu Pro Lys His Arg Val Ile
5 150 155 160

y Ser Gly Cys Asn Leu Asp Ser Ala Arg Phe Arg Tyr Leu Met Ala
165 170 175

J Lys Leu Gly Ile His Pro Ser Ser Cys His Gly Trp Ile Leu Gly
180 185 190

eolf-seql-S000001.txt

lu His Gly Asp Ser Ser Val Ala Val Trp Ser Gly Val Asn Val Ala
195 200 205

ly Val Ser Leu Gln Glu Leu Asn Pro Glu Met Gly Thr Asp Asn Asp
210 215 220

er Glu Asn Trp Lys Glu Val His Lys Met Val Val Glu Ser Ala Tyr
25 230 235 240

lu Val Ile Lys Leu Lys Gly Tyr Thr Asn Trp Ala Ile Gly Leu Ser
245 250 255

al Ala Asp Leu Ile Glu Ser Met Leu Lys Asn Leu Ser Arg Ile His
260 265 270

ro Val Ser Thr Met Val Lys Gly Met Tyr Gly Ile Glu Asn Glu Val
275 280 285

he Leu Ser Leu Pro Cys Ile Leu Asn Ala Arg Gly Leu Thr Ser Val
290 295 300

le Asn Gln Lys Leu Lys Asp Asp Glu Val Ala Gln Leu Lys Lys Ser
05 310 315 320

la Asp Thr Leu Trp Asp Ile Gln Lys Asp Leu Lys Asp Leu
325 330

10> 185
11> 343
12> PRT
13> Homo sapiens

00> 185

t Trp Pro Asn Gly Ser Ser Leu Gly Pro Cys Phe Arg Pro Thr Asn
5 10 15

e Thr Leu Glu Glu Arg Arg Leu Ile Ala Ser Pro Trp Phe Ala Ala
20 25 30

r Phe Cys Val Val Gly Leu Ala Ser Asn Leu Leu Ala Leu Ser Val
35 40 45

```
eu Ala Gly Ala Arg Gln Gly Gly Ser His Thr Arg Ser Ser Phe Leu
    50                  55                  60

nr Phe Leu Cys Gly Leu Val Leu Thr Asp Phe Leu Gly Leu Leu Val
5                   70                  75                  80

nr Gly Thr Ile Val Val Ser Gln His Ala Ala Leu Phe Glu Trp His
                85                  90                  95

la Val Asp Pro Gly Cys Arg Leu Cys Arg Phe Met Gly Val Val Met
            100                 105                 110

le Phe Phe Gly Leu Ser Pro Leu Leu Leu Gly Ala Ala Met Ala Ser
        115                 120                 125

lu Arg Tyr Leu Gly Ile Thr Arg Pro Phe Ser Arg Pro Ala Val Ala
    130                 135                 140

er Gln Arg Arg Ala Trp Ala Thr Val Gly Leu Val Trp Ala Ala Ala
15                  150                 155                 160

eu Ala Leu Gly Leu Leu Pro Leu Leu Gly Val Gly Arg Tyr Thr Val
                165                 170                 175

.n Tyr Pro Gly Ser Trp Cys Phe Leu Thr Leu Gly Ala Glu Ser Gly
            180                 185                 190

sp Val Ala Phe Gly Leu Leu Phe Ser Met Leu Gly Gly Leu Ser Val
        195                 200                 205

.y Leu Ser Phe Leu Leu Asn Thr Val Ser Val Ala Thr Leu Cys His
    210                 215                 220

.l Tyr His Gly Gln Glu Ala Ala Gln Gln Arg Pro Arg Asp Ser Glu
5                   230                 235                 240

.l Glu Met Met Ala Gln Leu Leu Gly Ile Met Val Val Ala Ser Val
                245                 250                 255

s Trp Leu Pro Leu Leu Val Phe Ile Ala Gln Thr Val Leu Arg Asn
            260                 265                 270
```

:o Pro Ala Met Ser Pro Ala Gly Gln Leu Ser Arg Thr Thr Glu Lys
275 280 285

lu Leu Leu Ile Tyr Leu Arg Val Ala Thr Trp Asn Gln Ile Leu Asp
290 295 300

:o Trp Val Tyr Ile Leu Phe Arg Arg Ala Val Leu Arg Arg Leu Gln
)5 310 315 320

:o Arg Leu Ser Thr Arg Pro Arg Ser Leu Ser Leu Gln Pro Gln Leu
325 330 335

ır Gln Arg Ser Gly Leu Gln
340

:10> 186
:11> 477
:12> PRT
:13> Homo sapiens

!00> 186

:t Ala Asn Met Gln Gly Leu Val Glu Arg Leu Glu Arg Ala Val Ser
5 10 15

'g Leu Glu Ser Leu Ser Ala Glu Ser His Arg Pro Pro Gly Asn Cys
20 25 30

.y Glu Val Asn Gly Val Ile Ala Gly Val Ala Pro Ser Val Glu Ala
35 40 45

.e Asp Lys Leu Met Asp Ser Met Val Ala Glu Phe Leu Lys Asn Ser
50 55 60

g Ile Leu Ala Gly Asp Val Glu Thr His Ala Glu Met Val His Ser
70 75 80

a Phe Gln Ala Gln Arg Ala Phe Leu Leu Met Ala Ser Gln Tyr Gln
85 90 95

n Pro His Glu Asn Asp Val Ala Ala Leu Leu Lys Pro Ile Ser Glu
100 105 110

/s Ile Gln Glu Ile Gln Thr Phe Arg Glu Arg Asn Arg Gly Ser Asn
115 120 125

et Phe Asn His Leu Ser Ala Val Ser Glu Ser Ile Pro Ala Leu Gly
130 135 140

:p Ile Ala Val Ser Pro Lys Pro Gly Pro Tyr Val Lys Glu Met Asn
l5 150 155 160

sp Ala Ala Thr Phe Tyr Thr Asn Arg Val Leu Lys Asp Tyr Lys His
165 170 175

er Asp Leu Arg His Val Asp Trp Val Lys Ser Tyr Leu Asn Ile Trp
180 185 190

er Glu Leu Gln Ala Tyr Ile Lys Glu His His Thr Thr Gly Leu Thr
195 200 205

'p Ser Lys Thr Gly Pro Val Ala Ser Thr Val Ser Ala Phe Ser Val
210 215 220

u Ser Ser Gly Pro Gly Leu Pro Pro Pro Pro Pro Pro Leu Pro Pro
5 230 235 240

'o Gly Pro Pro Pro Leu Phe Glu Asn Glu Gly Lys Lys Glu Glu Ser
245 250 255

r Pro Ser Arg Ser Ala Leu Phe Ala Gln Leu Asn Gln Gly Glu Ala
260 265 270

e Thr Lys Gly Leu Arg His Val Thr Asp Asp Gln Lys Thr Tyr Lys
275 280 285

n Pro Ser Leu Arg Ala Gln Gly Gly Gln Thr Gln Ser Pro Thr Lys
290 295 300

r His Thr Pro Ser Pro Thr Ser Pro Lys Ser Tyr Pro Ser Gln Lys
5 310 315 320

s Ala Pro Val Leu Glu Leu Glu Gly Lys Lys Trp Arg Val Glu Tyr
325 330 335

```
ln Glu Asp Arg Asn Asp Leu Val Ile Ser Glu Thr Glu Leu Lys Gln
           340                 345                 350

al Ala Tyr Ile Phe Lys Cys Glu Lys Ser Thr Ile Gln Ile Lys Gly
       355                 360                 365

ys Val Asn Ser Ile Ile Ile Asp Asn Cys Lys Lys Leu Gly Leu Val
   370                 375                 380

he Asp Asn Val Val Gly Ile Val Glu Val Ile Asn Ser Gln Asp Ile
35                 390                 395                 400

.n Ile Gln Val Met Gly Arg Val Pro Thr Ile Ser Ile Asn Lys Thr
               405                 410                 415

.u Gly Cys His Ile Tyr Leu Ser Glu Asp Ala Leu Asp Cys Glu Ile
           420                 425                 430

il Ser Ala Lys Ser Ser Glu Met Asn Ile Leu Ile Pro Gln Asp Gly
       435                 440                 445

sp Tyr Arg Glu Phe Pro Ile Pro Glu Gln Phe Lys Thr Ala Trp Asp
   450                 455                 460

.y Ser Lys Leu Ile Thr Glu Pro Ala Glu Ile Met Ala
:5                 470                 475


10>  187
11>  309
12>  PRT
13>  Homo sapiens

00>  187

t Asp Glu Lys Val Phe Thr Lys Glu Leu Asp Gln Trp Ile Glu Gln
              5                   10                  15

u Asn Glu Cys Lys Gln Leu Ser Glu Ser Gln Val Lys Ser Leu Cys
          20                  25                  30

u Lys Ala Lys Glu Ile Leu Thr Lys Glu Ser Asn Val Gln Glu Val
      35                  40                  45
```

```
rg Cys Pro Val Thr Val Cys Gly Asp Val His Gly Gln Phe His Asp
   50                  55                  60

eu Met Glu Leu Phe Arg Ile Gly Gly Lys Ser Pro Asp Thr Asn Tyr
5                  70                  75                  80

eu Phe Met Gly Asp Tyr Val Asp Arg Gly Tyr Tyr Ser Val Glu Thr
               85                  90                  95

al Thr Leu Leu Val Ala Leu Lys Val Arg Tyr Arg Glu Arg Ile Thr
           100                 105                 110

le Leu Arg Gly Asn His Glu Ser Arg Gln Ile Thr Gln Val Tyr Gly
       115                 120                 125

he Tyr Asp Glu Cys Leu Arg Lys Tyr Gly Asn Ala Asn Val Trp Lys
   130                 135                 140

yr Phe Thr Asp Leu Phe Asp Tyr Leu Pro Leu Thr Ala Leu Val Asp
45                 150                 155                 160

ly Gln Ile Phe Cys Leu His Gly Gly Leu Ser Pro Ser Ile Asp Thr
               165                 170                 175

eu Asp His Ile Arg Ala Leu Asp Arg Leu Gln Glu Val Pro His Glu
           180                 185                 190

ly Pro Met Cys Asp Leu Leu Trp Ser Asp Pro Asp Asp Arg Gly Gly
       195                 200                 205

sp Gly Ile Ser Pro Arg Gly Ala Gly Tyr Thr Phe Gly Gln Asp Ile
   210                 215                 220

er Glu Thr Phe Asn His Ala Asn Gly Leu Thr Leu Val Ser Arg Ala
25                 230                 235                 240

ys Gln Leu Val Met Glu Gly Tyr Asn Trp Cys His Asp Arg Asn Val
               245                 250                 255

al Thr Ile Phe Ser Ala Pro Asn Tyr Cys Tyr Arg Cys Gly Asn Gln
```

260 265 270

la Ala Ile Met Glu Leu Asp Asp Thr Leu Lys Tyr Ser Phe Leu Gln
275 280 285

he Asp Pro Ala Pro Arg Arg Gly Glu Pro His Val Thr Arg Arg Thr
290 295 300

ro Asp Tyr Phe Leu
)5

210> 188
211> 169
212> PRT
213> Homo sapiens

400> 188

et Ala Ala Leu Leu Leu Arg His Val Gly Arg His Cys Leu Arg Ala
5 10 15

is Phe Ser Pro Gln Leu Cys Ile Arg Asn Ala Val Pro Leu Gly Thr
20 25 30

ır Ala Lys Glu Glu Met Glu Arg Phe Trp Asn Lys Asn Ile Gly Ser
35 40 45

sn Arg Pro Leu Ser Pro His Ile Thr Ile Tyr Ser Trp Ser Leu Pro
50 55 60

et Ala Met Ser Ile Cys His Arg Gly Thr Gly Ile Ala Leu Ser Ala
5 70 75 80

.y Val Ser Leu Phe Gly Met Ser Ala Leu Leu Leu Pro Gly Asn Phe
85 90 95

.u Ser Tyr Leu Glu Leu Val Lys Ser Leu Cys Leu Gly Pro Ala Leu
100 105 110

.e His Thr Ala Lys Phe Ala Leu Val Phe Pro Leu Met Tyr His Thr
115 120 125

p Asn Gly Ile Arg His Leu Met Trp Asp Leu Gly Lys Gly Leu Lys

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130 135 140

le Pro Gln Leu Tyr Gln Ser Gly Val Val Val Leu Val Leu Thr Val
45 150 155 160

eu Ser Ser Met Gly Leu Ala Ala Met
165

210> 189
211> 201
212> PRT
213> Homo sapiens

400> 189

et Thr Glu Lys Ala Pro Glu Pro His Val Glu Glu Asp Asp Asp Asp
5 10 15

lu Leu Asp Ser Lys Leu Asn Tyr Lys Pro Pro Pro Gln Lys Ser Leu
20 25 30

's Glu Leu Gln Glu Met Asp Lys Asp Asp Glu Ser Leu Ile Lys Tyr
35 40 45

's Lys Thr Leu Leu Gly Asp Gly Pro Val Val Thr Asp Pro Lys Ala
50 55 60

o Asn Val Val Val Thr Arg Leu Thr Leu Val Cys Glu Ser Ala Pro
70 75 80

y Pro Ile Thr Met Asp Leu Thr Gly Asp Leu Glu Ala Leu Lys Lys
85 90 95

u Thr Ile Val Leu Lys Glu Gly Ser Glu Tyr Arg Val Lys Ile His
100 105 110

e Lys Val Asn Arg Asp Ile Val Ser Gly Leu Lys Tyr Val Gln His
115 120 125

: Tyr Arg Thr Gly Val Lys Val Asp Lys Ala Thr Phe Met Val Gly
130 135 140

: Tyr Gly Pro Arg Pro Glu Glu Tyr Glu Phe Leu Thr Pro Val Glu

15 150 155 160

lu Ala Pro Lys Gly Met Leu Ala Arg Gly Thr Tyr His Asn Lys Ser
165 170 175

le Phe Thr Asp Asp Asp Lys Gln Asp His Leu Ser Trp Glu Trp Asn
180 185 190

eu Ser Ile Lys Lys Glu Trp Thr Glu
195 200

<210> 190
<211> 377
<212> PRT
<213> Homo sapiens

<400> 190

et Lys Phe Pro Gly Pro Leu Glu Asn Gln Arg Leu Ser Phe Leu Leu
5 10 15

u Lys Ala Ile Thr Arg Glu Ala Gln Met Trp Lys Val Asn Val Arg
20 25 30

's Met Pro Ser Asn Gln Asn Val Ser Pro Ser Gln Arg Asp Glu Val
35 40 45

e Gln Trp Leu Ala Lys Leu Lys Tyr Gln Phe Asn Leu Tyr Pro Glu
50 55 60

r Phe Ala Leu Ala Ser Ser Leu Leu Asp Arg Phe Leu Ala Thr Val
70 75 80

s Ala His Pro Lys Tyr Leu Ser Cys Ile Ala Ile Ser Cys Phe Phe
85 90 95

u Ala Ala Lys Thr Val Glu Glu Asp Glu Arg Ile Pro Val Leu Lys
100 105 110

l Leu Ala Arg Asp Ser Phe Cys Gly Cys Ser Ser Ser Glu Ile Leu
115 120 125

g Met Glu Arg Ile Ile Leu Asp Lys Leu Asn Trp Asp Leu His Thr

130 135 140

.a Thr Pro Leu Asp Phe Leu His Ile Phe His Ala Ile Ala Val Ser
!5 150 155 160

ır Arg Pro Gln Leu Leu Phe Ser Leu Pro Lys Leu Ser Pro Ser Gln
165 170 175

.s Leu Ala Val Leu Thr Lys Gln Leu Leu His Cys Met Ala Cys Asn
180 185 190

.n Leu Leu Gln Phe Arg Gly Ser Met Leu Ala Leu Ala Met Val Ser
195 200 205

:u Glu Met Glu Lys Leu Ile Pro Asp Trp Leu Ser Leu Thr Ile Glu
210 215 220

:u Leu Gln Lys Ala Gln Met Asp Ser Ser Gln Leu Ile His Cys Arg
:5 230 235 240

.u Leu Val Ala His His Leu Ser Thr Leu Gln Ser Ser Leu Pro Leu
245 250 255

n Ser Val Tyr Val Tyr Arg Pro Leu Lys His Thr Leu Val Thr Cys
260 265 270

p Lys Gly Val Phe Arg Leu His Pro Ser Ser Val Pro Gly Pro Asp
275 280 285

e Ser Lys Asp Asn Ser Lys Pro Glu Val Pro Val Arg Gly Thr Ala
290 295 300

a Phe Tyr His His Leu Pro Ala Ala Ser Gly Cys Lys Gln Thr Ser
5 310 315 320

r Lys Arg Lys Val Glu Glu Met Glu Val Asp Asp Phe Tyr Asp Gly
325 330 335

e Lys Arg Leu Tyr Asn Glu Asp Asn Val Ser Glu Asn Val Gly Ser
340 345 350

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al Cys Gly Thr Asp Leu Ser Arg Gln Glu Gly His Ala Ser Pro Cys
355 360 365

ro Pro Leu Gln Pro Val Ser Val Met
370 375

210> 191
211> 282
212> PRT
213> Homo sapiens

400> 191

et Glu Arg Pro Ser Leu Arg Ala Leu Leu Leu Gly Ala Ala Gly Leu
5 10 15

eu Leu Leu Leu Leu Pro Leu Ser Ser Ser Ser Ser Ser Asp Thr Cys
20 25 30

ly Pro Cys Glu Pro Ala Ser Cys Pro Pro Leu Pro Pro Leu Gly Cys
35 40 45

eu Leu Gly Glu Thr Arg Asp Ala Cys Gly Cys Cys Pro Met Cys Ala
50 55 60

rg Gly Glu Gly Glu Pro Cys Gly Gly Gly Gly Ala Gly Arg Gly Tyr
5 70 75 80

's Ala Pro Gly Met Glu Cys Val Lys Ser Arg Lys Arg Arg Lys Gly
85 90 95

's Ala Gly Ala Ala Ala Gly Gly Pro Gly Val Ser Gly Val Cys Val
100 105 110

's Lys Ser Arg Tyr Pro Val Cys Gly Ser Asp Gly Thr Thr Tyr Pro
115 120 125

r Gly Cys Gln Leu Arg Ala Ala Ser Gln Arg Ala Glu Ser Arg Gly
130 135 140

u Lys Ala Ile Thr Gln Val Ser Lys Gly Thr Cys Glu Gln Gly Pro
5 150 155 160

```
er Ile Val Thr Pro Pro Lys Asp Ile Trp Asn Val Thr Gly Ala Gln
               165                     170                     175

al Tyr Leu Ser Cys Glu Val Ile Gly Ile Pro Thr Pro Val Leu Ile
           180                     185                     190

rp Asn Lys Val Lys Arg Gly His Tyr Gly Val Gln Arg Thr Glu Leu
       195                     200                     205

eu Pro Gly Asp Arg Asp Asn Leu Ala Ile Gln Thr Arg Gly Gly Pro
   210                     215                     220

.u Lys His Glu Val Thr Gly Trp Val Leu Val Ser Pro Leu Ser Lys
25                     230                     235                     240

.u Asp Ala Gly Glu Tyr Glu Cys His Ala Ser Asn Ser Gln Gly Gln
               245                     250                     255

.a Ser Ala Ser Ala Lys Ile Thr Val Val Asp Ala Leu His Glu Ile
           260                     265                     270

o Val Lys Lys Gly Glu Gly Ala Glu Leu
       275                     280


10>  192
11>  339
12>  PRT
13>  Homo sapiens

00>  192

t Asp Gln Asn Asn Ser Leu Pro Pro Tyr Ala Gln Gly Leu Ala Ser
               5                    10                      15

o Gln Gly Ala Met Thr Pro Gly Ile Pro Ile Phe Ser Pro Met Met
           20                      25                      30

o Tyr Gly Thr Gly Leu Thr Pro Gln Pro Ile Gln Asn Thr Asn Ser
       35                      40                      45

u Ser Ile Leu Glu Glu Gln Gln Arg Gln Gln Gln Gln Gln Gln Gln
   50                      55                      60
```

ln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
5 70 75 80

ln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Ala
85 90 95

al Ala Ala Ala Ala Val Gln Gln Ser Thr Ser Gln Gln Ala Thr Gln
100 105 110

ly Thr Ser Gly Gln Ala Pro Gln Leu Phe His Ser Gln Thr Leu Thr
115 120 125

hr Ala Pro Leu Pro Gly Thr Thr Pro Leu Tyr Pro Ser Pro Met Thr
130 135 140

ro Met Thr Pro Ile Thr Pro Ala Thr Pro Ala Ser Glu Ser Ser Gly
15 150 155 160

le Val Pro Gln Leu Gln Asn Ile Val Ser Thr Val Asn Leu Gly Cys
165 170 175

ys Leu Asp Leu Lys Thr Ile Ala Leu Arg Ala Arg Asn Ala Glu Tyr
180 185 190

sn Pro Lys Arg Phe Ala Ala Val Ile Met Arg Ile Arg Glu Pro Arg
195 200 205

hr Thr Ala Leu Ile Phe Ser Ser Gly Lys Met Val Cys Thr Gly Ala
210 215 220

ys Ser Glu Glu Gln Ser Arg Leu Ala Ala Arg Lys Tyr Ala Arg Val
25 230 235 240

l Gln Lys Leu Gly Phe Pro Ala Lys Phe Leu Asp Phe Lys Ile Gln
245 250 255

n Met Val Gly Ser Cys Asp Val Lys Phe Pro Ile Arg Leu Glu Gly
260 265 270

u Val Leu Thr His Gln Gln Phe Ser Ser Tyr Glu Pro Glu Leu Phe
275 280 285

ro Gly Leu Ile Tyr Arg Met Ile Lys Pro Arg Ile Val Leu Leu Ile
290 295 300

ne Val Ser Gly Lys Val Val Leu Thr Gly Ala Lys Val Arg Ala Glu
)5 310 315 320

le Tyr Glu Ala Phe Glu Asn Ile Tyr Pro Ile Leu Lys Gly Phe Arg
325 330 335

/s Thr Thr

?10> 193
?11> 184
?12> PRT
?13> Homo sapiens

100> 193

et Ala Ala Ala Gly Gly Ala Arg Leu Leu Arg Ala Ala Ser Ala Val
5 10 15

eu Gly Gly Pro Ala Gly Arg Trp Leu His His Ala Gly Ser Arg Ala
20 25 30

.y Ser Ser Gly Leu Leu Arg Asn Arg Gly Pro Gly Gly Ser Ala Glu
35 40 45

.a Ser Arg Ser Leu Ser Val Ser Ala Arg Ala Arg Ser Ser Ser Glu
50 55 60

sp Lys Ile Thr Val His Phe Ile Asn Arg Asp Gly Glu Thr Leu Thr
70 75 80

er Lys Gly Lys Val Gly Asp Ser Leu Leu Asp Val Val Val Glu Asn
85 90 95

n Leu Asp Ile Asp Gly Phe Gly Ala Cys Glu Gly Thr Leu Ala Cys
100 105 110

r Thr Cys His Leu Ile Phe Glu Asp His Ile Tyr Glu Lys Leu Asp
115 120 125

la Ile Thr Asp Glu Glu Asn Asp Met Leu Asp Leu Ala Tyr Gly Leu
130 135 140

ır Asp Arg Ser Arg Leu Gly Cys Gln Ile Cys Leu Thr Lys Ser Met
ɫ5 150 155 160

ɜp Asn Met Thr Val Arg Val Pro Glu Thr Val Ala Asp Ala Arg Gln
165 170 175

ɜr Ile Asp Val Gly Lys Thr Ser
180

ʔ10> 194
ʔ11> 206
ʔ12> PRT
ʔ13> Homo sapiens

ɟ00> 194

ɜt Thr Ala Ser Val Leu Arg Ser Ile Ser Leu Ala Leu Arg Pro Thr
5 10 15

ɜr Gly Leu Leu Gly Thr Trp Gln Thr Gln Leu Arg Glu Thr His Gln
20 25 30

:g Ala Ser Leu Leu Ser Phe Trp Glu Leu Ile Pro Met Arg Ser Glu
35 40 45

:o Leu Arg Lys Lys Lys Lys Val Asp Pro Lys Lys Asp Gln Glu Ala
50 55 60

's Glu Arg Leu Lys Arg Lys Ile Arg Lys Leu Glu Lys Ala Thr Gln
ʻ 70 75 80

.u Leu Ile Pro Ile Glu Asp Phe Ile Thr Pro Leu Lys Phe Leu Asp
85 90 95

's Ala Arg Glu Arg Pro Gln Val Glu Leu Thr Phe Glu Glu Thr Glu
100 105 110

g Arg Ala Leu Leu Leu Lys Lys Trp Ser Leu Tyr Lys Gln Gln Glu
115 120 125

rg Lys Met Glu Arg Asp Thr Ile Arg Ala Met Leu Glu Ala Gln Gln
130 135 140

lu Ala Leu Glu Glu Leu Gln Leu Glu Ser Pro Lys Leu His Ala Glu
45 150 155 160

la Ile Lys Arg Asp Pro Asn Leu Phe Pro Phe Glu Lys Glu Gly Pro
165 170 175

is Tyr Thr Pro Pro Ile Pro Asn Tyr Gln Pro Pro Glu Gly Arg Tyr
180 185 190

sn Asp Ile Thr Lys Val Tyr Thr Gln Val Glu Phe Lys Arg
195 200 205

:10> 195
:11> 75
:12> PRT
:13> Homo sapiens

!00> 195

:t Lys Gly Glu Thr Pro Val Asn Ser Thr Met Ser Ile Gly Gln Ala
5 10 15

:g Lys Met Val Glu Gln Leu Lys Ile Glu Ala Ser Leu Cys Arg Ile
20 25 30

's Val Ser Lys Ala Ala Ala Asp Leu Met Thr Tyr Cys Asp Ala His
35 40 45

a Cys Glu Asp Pro Leu Ile Thr Pro Val Pro Thr Ser Glu Asn Pro
50 55 60

e Arg Glu Lys Lys Phe Phe Cys Ala Leu Leu
70 75

10> 196
11> 317
12> PRT
13> Homo sapiens

00> 196

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```
et Arg Leu Gly Pro Arg Thr Ala Ala Leu Gly Leu Leu Leu Leu Cys
               5                   10                  15

la Ala Ala Ala Gly Ala Gly Lys Ala Glu Glu Leu His Tyr Pro Leu
            20                  25                  30

ly Glu Arg Arg Ser Asp Tyr Asp Arg Glu Ala Leu Leu Gly Val Gln
        35                  40                  45

lu Asp Val Asp Glu Tyr Val Lys Leu Gly His Glu Glu Gln Gln Lys
    50                  55                  60

rg Leu Gln Ala Ile Ile Lys Lys Ile Asp Leu Asp Ser Asp Gly Phe
5                   70                  75                  80

eu Thr Glu Ser Glu Leu Ser Ser Trp Ile Gln Met Ser Phe Lys His
               85                  90                  95

yr Ala Met Gln Glu Ala Lys Gln Gln Phe Val Glu Tyr Asp Lys Asn
            100                 105                 110

er Asp Asp Thr Val Thr Trp Asp Glu Tyr Asn Ile Gln Met Tyr Asp
        115                 120                 125

rg Val Ile Asp Phe Asp Glu Asn Thr Ala Leu Asp Asp Ala Glu Glu
    130                 135                 140

u Ser Phe Arg Lys Leu His Leu Lys Asp Lys Lys Arg Phe Glu Lys
15                  150                 155                 160

a Asn Gln Asp Ser Gly Pro Gly Leu Ser Leu Glu Glu Phe Ile Ala
               165                 170                 175

ie Glu His Pro Glu Glu Val Asp Tyr Met Thr Glu Phe Val Ile Gln
            180                 185                 190

u Ala Leu Glu Glu His Asp Lys Asn Gly Asp Gly Phe Val Ser Leu
        195                 200                 205

u Glu Phe Leu Gly Asp Tyr Arg Trp Asp Pro Thr Ala Asn Glu Asp
    210                 215                 220
```

ro Glu Trp Ile Leu Val Glu Lys Asp Arg Phe Val Asn Asp Tyr Asp
25 230 235 240

ys Asp Asn Asp Gly Arg Leu Asp Pro Gln Glu Leu Leu Pro Trp Val
245 250 255

al Pro Asn Asn Gln Gly Ile Ala Gln Glu Glu Ala Leu His Leu Ile
260 265 270

sp Glu Met Asp Leu Asn Gly Asp Lys Lys Leu Ser Glu Glu Glu Ile
275 280 285

eu Glu Asn Pro Asp Leu Phe Leu Thr Ser Glu Ala Thr Asp Tyr Gly
290 295 300

rg Gln Leu His Asp Asp Tyr Phe Tyr His Asp Glu Leu
05 310 315

210> 197
211> 239
212> PRT
213> Homo sapiens

400> 197

et Ala Pro Ser Val Pro Ala Ala Glu Pro Glu Tyr Pro Lys Gly Ile
5 10 15

rg Ala Val Leu Leu Gly Pro Pro Gly Ala Gly Lys Gly Thr Gln Ala
20 25 30

ro Arg Leu Ala Glu Asn Phe Cys Val Cys His Leu Ala Thr Gly Asp
35 40 45

et Leu Arg Ala Met Val Ala Ser Gly Ser Glu Leu Gly Lys Lys Leu
50 55 60

s Ala Thr Met Asp Ala Gly Lys Leu Val Ser Asp Glu Met Val Val
70 75 80

u Leu Ile Glu Lys Asn Leu Glu Thr Pro Leu Cys Lys Asn Gly Phe
85 90 95

eu Leu Asp Gly Phe Pro Arg Thr Val Arg Gln Ala Glu Met Leu Asp
100 105 110

sp Leu Met Glu Lys Arg Lys Glu Lys Leu Asp Ser Val Ile Glu Phe
115 120 125

er Ile Pro Asp Ser Leu Leu Ile Arg Arg Ile Thr Gly Arg Leu Ile
130 135 140

is Pro Lys Ser Gly Arg Ser Tyr His Glu Glu Phe Asn Pro Pro Lys
45 150 155 160

lu Pro Met Lys Asp Asp Ile Thr Gly Glu Pro Leu Ile Arg Arg Ser
165 170 175

sp Asp Asn Glu Lys Ala Leu Lys Ile Arg Leu Gln Ala Tyr His Thr
180 185 190

ln Thr Thr Pro Leu Ile Glu Tyr Tyr Arg Lys Arg Gly Ile His Ser
195 200 205

la Ile Asp Ala Ser Gln Thr Pro Asp Val Val Phe Ala Ser Ile Leu
210 215 220

.a Ala Phe Ser Lys Ala Thr Cys Lys Asp Leu Val Met Phe Ile
25 230 235

:10> 198
:11> 217
:12> PRT
:13> Homo sapiens

:00> 198

:t Ser Ser Lys Val Ser Arg Asp Thr Leu Tyr Glu Ala Val Arg Glu
5 10 15

.l Leu His Gly Asn Gln Arg Lys Arg Arg Lys Phe Leu Glu Thr Val
20 25 30

u Leu Gln Ile Ser Leu Lys Asn Tyr Asp Pro Gln Lys Asp Lys Arg
35 40 45

he Ser Gly Thr Val Arg Leu Lys Ser Thr Pro Arg Pro Lys Phe Ser
50 55 60

al Cys Val Leu Gly Asp Gln Gln His Cys Asp Glu Ala Lys Ala Val
5 70 75 80

sp Ile Pro His Met Asp Ile Glu Ala Leu Lys Lys Leu Asn Lys Asn
85 90 95

ys Lys Leu Val Lys Lys Leu Ala Lys Lys Tyr Asp Ala Phe Leu Ala
100 105 110

er Glu Ser Leu Ile Lys Gln Ile Pro Arg Ile Leu Gly Pro Gly Leu
115 120 125

sn Lys Ala Gly Lys Phe Pro Ser Leu Leu Thr His Asn Glu Asn Met
130 135 140

al Ala Lys Val Asp Glu Val Lys Ser Thr Ile Lys Phe Gln Met Lys
15 150 155 160

ys Val Leu Cys Leu Ala Val Ala Val Gly His Val Lys Met Thr Asp
165 170 175

sp Glu Leu Val Tyr Asn Ile His Leu Ala Val Asn Phe Leu Val Ser
180 185 190

eu Leu Lys Lys Asn Trp Gln Asn Val Arg Ala Leu Tyr Ile Lys Ser
195 200 205

ır Met Gly Lys Pro Gln Arg Leu Tyr
210 215

:10> 199
:11> 150
:12> PRT
:13> Homo sapiens

00> 199

:t Ser Lys Ile Ser Gln Gln Asn Ser Thr Pro Gly Val Asn Gly Ile
5 10 15

```
er Val Ile His Thr Gln Ala His Ala Ser Gly Leu Gln Gln Val Pro
            20                  25                  30

ln Leu Val Pro Ala Gly Pro Gly Gly Gly Gly Lys Ala Val Ala Pro
        35                  40                  45

er Lys Gln Ser Lys Lys Ser Ser Pro Met Asp Arg Asn Ser Asp Glu
    50                  55                  60

yr Arg Gln Arg Arg Glu Arg Asn Asn Met Ala Val Lys Lys Ser Arg
5                   70                  75                  80

eu Lys Ser Lys Gln Lys Ala Gln Asp Thr Leu Gln Arg Val Asn Gln
                85                  90                  95

eu Lys Glu Glu Asn Glu Arg Leu Glu Ala Lys Ile Lys Leu Leu Thr
            100                 105                 110

ys Glu Leu Ser Val Leu Lys Asp Leu Phe Leu Glu His Ala His Asn
        115                 120                 125

eu Ala Asp Asn Val Gln Ser Ile Ser Thr Glu Asn Thr Thr Ala Asp
    130                 135                 140

ly Asp Asn Ala Gly Gln
15                  150

:10>  200
:11>  331
:12>  PRT
:13>  Homo sapiens

100>  200

et Gly Thr Pro Gln Lys Asp Val Ile Ile Lys Ser Asp Ala Pro Asp
                5                   10                  15

ır Leu Leu Leu Glu Lys His Ala Asp Tyr Ile Ala Ser Tyr Gly Ser
            20                  25                  30

's Lys Asp Asp Tyr Glu Tyr Cys Met Ser Glu Tyr Leu Arg Met Ser
        35                  40                  45
```

```
ly Ile Tyr Trp Gly Leu Thr Val Met Asp Leu Met Gly Gln Leu His
   50                  55                  60

rg Met Asn Arg Glu Glu Ile Leu Ala Phe Ile Lys Ser Cys Gln His
5                  70                  75                  80

lu Cys Gly Gly Ile Ser Ala Ser Ile Gly His Asp Pro His Leu Leu
               85                  90                  95

yr Thr Leu Ser Ala Val Gln Ile Leu Thr Leu Tyr Asp Ser Ile Asn
           100                 105                 110

al Ile Asp Val Asn Lys Val Val Glu Tyr Val Lys Gly Leu Gln Lys
       115                 120                 125

lu Asp Gly Ser Phe Ala Gly Asp Ile Trp Gly Glu Ile Asp Thr Arg
   130                 135                 140

ne Ser Phe Cys Ala Val Ala Thr Leu Ala Leu Leu Gly Lys Leu Asp
45                 150                 155                 160

la Ile Asn Val Glu Lys Ala Ile Glu Phe Val Leu Ser Cys Met Asn
               165                 170                 175

ne Asp Gly Gly Phe Gly Cys Arg Pro Gly Ser Glu Ser His Ala Gly
           180                 185                 190

ln Ile Tyr Cys Cys Thr Gly Phe Leu Ala Ile Thr Ser Gln Leu His
       195                 200                 205

.n Val Asn Ser Asp Leu Leu Gly Trp Trp Leu Cys Glu Arg Gln Leu
   210                 215                 220

ro Ser Gly Gly Leu Asn Gly Arg Pro Glu Lys Leu Pro Asp Val Cys
25                 230                 235                 240

'r Ser Trp Trp Val Leu Ala Ser Leu Lys Ile Ile Gly Arg Leu His
               245                 250                 255

p Ile Asp Arg Glu Lys Leu Arg Asn Phe Ile Leu Ala Cys Gln Asp
           260                 265                 270
```

lu Glu Thr Gly Gly Phe Ala Asp Arg Pro Gly Asp Met Val Asp Pro
275 280 285

he His Thr Leu Phe Gly Ile Ala Gly Leu Ser Leu Leu Gly Glu Glu
290 295 300

ln Ile Lys Pro Val Asn Pro Val Phe Cys Met Pro Glu Glu Val Leu
05 310 315 320

ln Arg Val Asn Val Gln Pro Glu Leu Val Ser
325 330

210> 201
211> 537
212> PRT
213> Homo sapiens

400> 201

et Gly Cys Val Gln Cys Lys Asp Lys Glu Ala Thr Lys Leu Thr Glu
5 10 15

lu Arg Asp Gly Ser Leu Asn Gln Ser Ser Gly Tyr Arg Tyr Gly Thr
20 25 30

sp Pro Thr Pro Gln His Tyr Pro Ser Phe Gly Val Thr Ser Ile Pro
35 40 45

sn Tyr Asn Asn Phe His Ala Ala Gly Gly Gln Gly Leu Thr Val Phe
50 55 60

ly Gly Val Asn Ser Ser Ser His Thr Gly Thr Leu Arg Thr Arg Gly
5 70 75 80

y Thr Gly Val Thr Leu Phe Val Ala Leu Tyr Asp Tyr Glu Ala Arg
85 90 95

ır Glu Asp Asp Leu Ser Phe His Lys Gly Glu Lys Phe Gln Ile Leu
100 105 110

n Ser Ser Glu Gly Asp Trp Trp Glu Ala Arg Ser Leu Thr Thr Gly
115 120 125

lu Thr Gly Tyr Ile Pro Ser Asn Tyr Val Ala Pro Val Asp Ser Ile
130 135 140

ln Ala Glu Glu Trp Tyr Phe Gly Lys Leu Gly Arg Lys Asp Ala Glu
45 150 155 160

rg Gln Leu Leu Ser Phe Gly Asn Pro Arg Gly Thr Phe Leu Ile Arg
165 170 175

lu Ser Glu Thr Thr Lys Gly Ala Tyr Ser Leu Ser Ile Arg Asp Trp
180 185 190

sp Asp Met Lys Gly Asp His Val Lys His Tyr Lys Ile Arg Lys Leu
195 200 205

sp Asn Gly Gly Tyr Tyr Ile Thr Thr Arg Ala Gln Phe Glu Thr Leu
210 215 220

ln Gln Leu Val Gln His Tyr Ser Glu Arg Ala Ala Gly Leu Cys Cys
25 230 235 240

rg Leu Val Val Pro Cys His Lys Gly Met Pro Arg Leu Thr Asp Leu
245 250 255

er Val Lys Thr Lys Asp Val Trp Glu Ile Pro Arg Glu Ser Leu Gln
260 265 270

eu Ile Lys Arg Leu Gly Asn Gly Gln Phe Gly Glu Val Trp Met Gly
275 280 285

hr Trp Asn Gly Asn Thr Lys Val Ala Ile Lys Thr Leu Lys Pro Gly
290 295 300

hr Met Ser Pro Glu Ser Phe Leu Glu Glu Ala Gln Ile Met Lys Lys
05 310 315 320

eu Lys His Asp Lys Leu Val Gln Leu Tyr Ala Val Val Ser Glu Glu
325 330 335

ro Ile Tyr Ile Val Thr Glu Tyr Met Asn Lys Gly Ser Leu Leu Asp

340 345 350

he Leu Lys Asp Gly Glu Gly Arg Ala Leu Lys Leu Pro Asn Leu Val
355 360 365

sp Met Ala Ala Gln Val Ala Ala Gly Met Ala Tyr Ile Glu Arg Met
370 375 380

sn Tyr Ile His Arg Asp Leu Arg Ser Ala Asn Ile Leu Val Gly Asn
85 390 395 400

ly Leu Ile Cys Lys Ile Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu
405 410 415

sp Asn Glu Tyr Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp
420 425 430

ır Ala Pro Glu Ala Ala Leu Tyr Gly Arg Phe Thr Ile Lys Ser Asp
435 440 445

al Trp Ser Phe Gly Ile Leu Leu Thr Glu Leu Val Thr Lys Gly Arg
450 455 460

al Pro Tyr Pro Gly Met Asn Asn Arg Glu Val Leu Glu Gln Val Glu
55 470 475 480

:g Gly Tyr Arg Met Pro Cys Pro Gln Asp Cys Pro Ile Ser Leu His
485 490 495

.u Leu Met Ile His Cys Trp Lys Lys Asp Pro Glu Glu Arg Pro Thr
500 505 510

ıe Glu Tyr Leu Gln Ser Phe Leu Glu Asp Tyr Phe Thr Ala Thr Glu
515 520 525

:o Gln Tyr Gln Pro Gly Glu Asn Leu
530 535

:10> 202
:11> 534
:12> PRT
:13> Homo sapiens

eolf-seql-S000001.txt

400> 202

et Gly Cys Val Gln Cys Lys Asp Lys Glu Ala Thr Lys Leu Thr Glu
5 10 15

lu Arg Asp Gly Ser Leu Asn Gln Ser Ser Gly Tyr Arg Tyr Gly Thr
20 25 30

sp Pro Thr Pro Gln His Tyr Pro Ser Phe Gly Val Thr Ser Ile Pro
35 40 45

sn Tyr Asn Asn Phe His Ala Ala Gly Gly Gln Gly Leu Thr Val Phe
50 55 60

ly Gly Val Asn Ser Ser Ser His Thr Gly Thr Leu Arg Thr Arg Gly
5 70 75 80

.y Thr Gly Val Thr Leu Phe Val Ala Leu Tyr Asp Tyr Glu Ala Arg
85 90 95

ır Glu Asp Asp Leu Ser Phe His Lys Gly Glu Lys Phe Gln Ile Leu
100 105 110

sn Ser Ser Glu Gly Asp Trp Trp Glu Ala Arg Ser Leu Thr Thr Gly
115 120 125

.u Thr Gly Tyr Ile Pro Ser Asn Tyr Val Ala Pro Val Asp Ser Ile
130 135 140

.n Ala Glu Glu Trp Tyr Phe Gly Lys Leu Gly Arg Lys Asp Ala Glu
5 150 155 160

g Gln Leu Leu Ser Phe Gly Asn Pro Arg Gly Thr Phe Leu Ile Arg
165 170 175

u Ser Glu Thr Thr Lys Gly Ala Tyr Ser Leu Ser Ile Arg Asp Trp
180 185 190

p Asp Met Lys Gly Asp His Val Lys His Tyr Lys Ile Arg Lys Leu
195 200 205

p Asn Gly Gly Tyr Tyr Ile Thr Thr Arg Ala Gln Phe Glu Thr Leu
210 215 220

n Gln Leu Val Gln His Tyr Ser Glu Lys Ala Asp Gly Leu Cys Phe
5 230 235 240

n Leu Thr Val Ile Ala Ser Ser Cys Thr Pro Gln Thr Ser Gly Leu
245 250 255

a Lys Asp Ala Trp Glu Val Ala Arg Arg Ser Leu Cys Leu Glu Lys
260 265 270

s Leu Gly Gln Gly Cys Phe Ala Glu Val Trp Leu Gly Thr Trp Asn
275 280 285

y Asn Thr Lys Val Ala Ile Lys Thr Leu Lys Pro Gly Thr Met Ser
290 295 300

) Glu Ser Phe Leu Glu Glu Ala Gln Ile Met Lys Lys Leu Lys His
5 310 315 320

) Lys Leu Val Gln Leu Tyr Ala Val Val Ser Glu Glu Pro Ile Tyr
325 330 335

: Val Thr Glu Tyr Met Asn Lys Gly Ser Leu Leu Asp Phe Leu Lys
340 345 350

) Gly Glu Gly Arg Ala Leu Lys Leu Pro Asn Leu Val Asp Met Ala
355 360 365

. Gln Val Ala Ala Gly Met Ala Tyr Ile Glu Arg Met Asn Tyr Ile
370 375 380

Arg Asp Leu Arg Ser Ala Asn Ile Leu Val Gly Asn Gly Leu Ile
390 395 400

Lys Ile Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu Asp Asn Glu
405 410 415

Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro
420 425 430

eolf-seql-S000001.txt

Ala Ala Leu Tyr Gly Arg Phe Thr Ile Lys Ser Asp Val Trp Ser
435 440 445

Gly Ile Leu Leu Thr Glu Leu Val Thr Lys Gly Arg Val Pro Tyr
450 455 460

Gly Met Asn Asn Arg Glu Val Leu Glu Gln Val Glu Arg Gly Tyr
470 475 480

Met Pro Cys Pro Gln Asp Cys Pro Ile Ser Leu His Glu Leu Met
485 490 495

His Cys Trp Lys Lys Asp Pro Glu Glu Arg Pro Thr Phe Glu Tyr
500 505 510

Gln Ser Phe Leu Glu Asp Tyr Phe Thr Ala Thr Glu Pro Gln Tyr
515 520 525

Pro Gly Glu Asn Leu
530

)> 203
l> 482
2> PRT
3> Homo sapiens

)> 203

Gly Cys Val Gln Cys Lys Asp Lys Glu Ala Thr Lys Leu Thr Glu
5 10 15

Arg Asp Gly Ser Leu Asn Gln Ser Ser Gly Tyr Arg Tyr Gly Thr
20 25 30

Pro Thr Pro Gln His Tyr Pro Ser Phe Gly Val Thr Ser Ile Pro
35 40 45

Tyr Asn Asn Phe His Ala Ala Gly Gly Gln Gly Leu Thr Val Phe
50 55 60

Gly Val Asn Ser Ser Ser His Thr Gly Thr Leu Arg Thr Arg Gly
70 75 80

Thr Gly Val Thr Leu Phe Val Ala Leu Tyr Asp Tyr Glu Ala Arg
85 90 95

Glu Asp Asp Leu Ser Phe His Lys Gly Glu Lys Phe Gln Ile Leu
100 105 110

Ser Ser Glu Gly Asp Trp Trp Glu Ala Arg Ser Leu Thr Thr Gly
115 120 125

Thr Gly Tyr Ile Pro Ser Asn Tyr Val Ala Pro Val Asp Ser Ile
130 135 140

Ala Glu Glu Trp Tyr Phe Gly Lys Leu Gly Arg Lys Asp Ala Glu
150 155 160

Gln Leu Leu Ser Phe Gly Asn Pro Arg Gly Thr Phe Leu Ile Arg
165 170 175

Ser Glu Thr Thr Lys Gly Ala Tyr Ser Leu Ser Ile Arg Asp Trp
180 185 190

Asp Met Lys Gly Asp His Val Lys His Tyr Lys Ile Arg Lys Leu
195 200 205

Asn Gly Gly Tyr Tyr Ile Thr Thr Arg Ala Gln Phe Glu Thr Leu
210 215 220

Gln Leu Val Gln His Tyr Ser Gly Thr Trp Asn Gly Asn Thr Lys
230 235 240

Ala Ile Lys Thr Leu Lys Pro Gly Thr Met Ser Pro Glu Ser Phe
245 250 255

Glu Glu Ala Gln Ile Met Lys Lys Leu Lys His Asp Lys Leu Val
260 265 270

Leu Tyr Ala Val Val Ser Glu Glu Pro Ile Tyr Ile Val Thr Glu
275 280 285

Met Asn Lys Gly Ser Leu Leu Asp Phe Leu Lys Asp Gly Glu Gly
290 295 300

Ala Leu Lys Leu Pro Asn Leu Val Asp Met Ala Ala Gln Val Ala
310 315 320

Gly Met Ala Tyr Ile Glu Arg Met Asn Tyr Ile His Arg Asp Leu
325 330 335

Ser Ala Asn Ile Leu Val Gly Asn Gly Leu Ile Cys Lys Ile Ala
340 345 350

Phe Gly Leu Ala Arg Leu Ile Glu Asp Asn Glu Tyr Thr Ala Arg
355 360 365

Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ala Leu
370 375 380

Gly Arg Phe Thr Ile Lys Ser Asp Val Trp Ser Phe Gly Ile Leu
390 395 400

Thr Glu Leu Val Thr Lys Gly Arg Val Pro Tyr Pro Gly Met Asn
405 410 415

Arg Glu Val Leu Glu Gln Val Glu Arg Gly Tyr Arg Met Pro Cys
420 425 430

Gln Asp Cys Pro Ile Ser Leu His Glu Leu Met Ile His Cys Trp
435 440 445

Lys Asp Pro Glu Glu Arg Pro Thr Phe Glu Tyr Leu Gln Ser Phe
450 455 460

Glu Asp Tyr Phe Thr Ala Thr Glu Pro Gln Tyr Gln Pro Gly Glu
470 475 480

Leu

0> 204
1> 674
2> PRT
3> Homo sapiens

)0> 204

: Ala Pro Gly Gln Ala Pro His Gln Ala Thr Pro Trp Arg Asp Ala
5 10 15

; Pro Phe Phe Leu Leu Ser Pro Val Met Gly Leu Leu Ser Arg Ala
20 25 30

› Ser Arg Leu Arg Gly Leu Gly Pro Leu Glu Pro Trp Leu Val Glu
35 40 45

ι Val Lys Gly Ala Ala Leu Val Glu Ala Gly Leu Glu Gly Glu Ala
50 55 60

ſ Thr Pro Leu Ala Ile Pro His Thr Pro Trp Gly Arg Arg Pro Gly
70 75 80

ι Glu Ala Glu Asp Ser Gly Gly Pro Gly Glu Asp Arg Glu Thr Leu
85 90 95

' Leu Lys Thr Ser Ser Ser Leu Pro Glu Ala Trp Gly Leu Leu Asp
100 105 110

› Asp Asp Gly Met Tyr Gly Glu Arg Glu Ala Thr Ser Val Pro Arg
115 120 125

Gln Gly Ser Gln Phe Ala Asp Gly Gln Arg Ala Pro Leu Ser Pro
130 135 140

Leu Leu Ile Arg Thr Leu Gln Gly Ser Asp Lys Asn Pro Gly Glu
150 155 160

Lys Ala Glu Glu Glu Gly Val Ala Glu Glu Glu Gly Val Asn Lys
165 170 175

Ser Tyr Pro Pro Ser His Arg Glu Cys Cys Pro Ala Val Glu Glu
180 185 190

Asp Asp Glu Glu Ala Val Lys Lys Glu Ala His Arg Thr Ser Thr
195 200 205

Ala Leu Ser Pro Gly Ser Lys Pro Ser Thr Trp Val Ser Cys Pro

210 215 220

ly Glu Glu Glu Asn Gln Ala Thr Glu Asp Lys Arg Thr Glu Arg Ser
25 230 235 240

ys Gly Ala Arg Lys Thr Ser Val Ser Pro Arg Ser Ser Gly Ser Asp
245 250 255

ro Arg Ser Trp Glu Tyr Arg Ser Gly Glu Ala Ser Glu Glu Lys Glu
260 265 270

lu Lys Ala His Glu Glu Thr Gly Lys Gly Glu Ala Ala Pro Gly Pro
275 280 285

.n Ser Ser Ala Pro Ala Gln Arg Pro Gln Leu Lys Ser Trp Trp Cys
290 295 300

.n Pro Ser Asp Glu Glu Glu Ser Glu Val Lys Pro Leu Gly Ala Ala
5 310 315 320

u Lys Asp Gly Glu Ala Glu Cys Pro Pro Cys Ile Pro Pro Pro Ser
325 330 335

a Phe Leu Lys Ala Trp Val Tyr Trp Pro Gly Glu Asp Thr Glu Glu
340 345 350

ı Glu Asp Glu Glu Glu Asp Glu Asp Ser Asp Ser Gly Ser Asp Glu
355 360 365

ı Glu Gly Glu Ala Glu Ala Ser Ser Ser Thr Pro Ala Thr Gly Val
370 375 380

: Leu Lys Ser Trp Val Tyr Gln Pro Gly Glu Asp Thr Glu Glu Glu
; 390 395 400

. Asp Glu Asp Ser Asp Thr Gly Ser Ala Glu Asp Glu Arg Glu Ala
405 410 415

Thr Ser Ala Ser Thr Pro Pro Ala Ser Ala Phe Leu Lys Ala Trp
420 425 430

```
Tyr Arg Pro Gly Glu Asp Thr Glu Glu Glu Glu Asp Glu Asp Val
    435                 440                 445

Ser Glu Asp Lys Glu Asp Asp Ser Glu Ala Ala Leu Gly Glu Ala
450                 455                 460

Ser Asp Pro His Pro Ser His Pro Asp Gln Ser Ala His Phe Arg
                470                 475                 480

Trp Gly Tyr Arg Pro Gly Lys Glu Thr Glu Glu Glu Glu Ala Ala
            485                 490                 495

Asp Trp Gly Glu Ala Glu Pro Cys Pro Phe Arg Val Ala Ile Tyr
        500                 505                 510

Pro Gly Glu Lys Pro Pro Pro Pro Trp Ala Pro Pro Arg Leu Pro
    515                 520                 525

Arg Leu Gln Arg Arg Leu Lys Arg Pro Glu Thr Pro Thr His Asp
530                 535                 540

Asp Pro Glu Thr Pro Leu Lys Ala Arg Lys Val Arg Phe Ser Glu
                550                 555                 560

Val Thr Val His Phe Leu Ala Val Trp Ala Gly Pro Ala Gln Ala
            565                 570                 575

Arg Gln Gly Pro Trp Glu Gln Leu Ala Arg Asp Arg Ser Arg Phe
        580                 585                 590

Arg Arg Ile Ala Gln Ala Gln Glu Glu Leu Ser Pro Cys Leu Thr
    595                 600                 605

Ala Ala Arg Ala Arg Ala Trp Ala Arg Leu Arg Asn Pro Pro Leu
610                 615                 620

Pro Ile Pro Ala Leu Thr Gln Thr Leu Pro Ser Ser Ser Val Pro
                630                 635                 640

Ser Pro Val Gln Thr Thr Pro Leu Ser Gln Ala Val Ala Thr Pro
            645                 650                 655
```

: Arg Ser Ser Ala Ala Ala Ala Ala Ala Leu Asp Leu Ser Gly Arg
660 665 670

r Gly

.0> 205
.1> 635
2> PRT
3> Homo sapiens

0> 205

Ser Val Gly Val Ser Thr Ser Ala Pro Leu Ser Pro Thr Ser Gly
5 10 15

Ser Val Gly Met Ser Thr Phe Ser Ile Met Asp Tyr Val Val Phe
20 25 30

Leu Leu Leu Val Leu Ser Leu Ala Ile Gly Leu Tyr His Ala Cys
35 40 45

Gly Trp Gly Arg His Thr Val Gly Glu Leu Leu Met Ala Asp Arg
50 55 60

Met Gly Cys Leu Pro Val Ala Leu Ser Leu Leu Ala Thr Phe Gln
70 75 80

Ala Val Ala Ile Leu Gly Val Pro Ser Glu Ile Tyr Arg Phe Gly
85 90 95

Gln Tyr Trp Phe Leu Gly Cys Cys Tyr Phe Leu Gly Leu Leu Ile
100 105 110

Ala His Ile Phe Ile Pro Val Phe Tyr Arg Leu His Leu Thr Ser
115 120 125

Tyr Glu Tyr Leu Glu Leu Arg Phe Asn Lys Thr Val Arg Val Cys
130 135 140

Thr Val Thr Phe Ile Phe Gln Met Val Ile Tyr Met Gly Val Val
150 155 160

Tyr Ala Pro Ser Leu Ala Leu Asn Ala Val Thr Gly Phe Asp Leu
165 170 175

Leu Ser Val Leu Ala Leu Gly Ile Val Cys Thr Val Tyr Thr Ala
180 185 190

Gly Gly Leu Lys Ala Val Ile Trp Thr Asp Val Phe Gln Thr Leu
195 200 205

Met Phe Leu Gly Gln Leu Ala Val Ile Ile Val Gly Ser Ala Lys
210 215 220

Gly Gly Leu Gly Arg Val Trp Ala Val Ala Ser Gln His Gly Arg
230 235 240

Ser Gly Phe Glu Leu Asp Pro Asp Pro Phe Val Arg His Thr Phe
245 250 255

Thr Leu Ala Phe Gly Gly Val Phe Met Met Leu Ser Leu Tyr Gly
260 265 270

Asn Gln Ala Gln Val Gln Arg Tyr Leu Ser Ser Arg Thr Glu Lys
275 280 285

Ala Val Leu Ser Cys Tyr Ala Val Phe Pro Phe Gln Gln Val Ser
290 295 300

Cys Val Gly Cys Leu Ile Gly Leu Val Met Phe Ala Tyr Tyr Gln
310 315 320

Tyr Pro Met Ser Ile Gln Gln Ala Gln Ala Ala Pro Asp Gln Phe
325 330 335

Leu Tyr Phe Val Met Asp Leu Leu Lys Gly Leu Pro Gly Leu Pro
340 345 350

Leu Phe Ile Ala Cys Leu Phe Ser Gly Ser Leu Ser Thr Ile Ser
355 360 365

Ala Phe Asn Ser Leu Ala Thr Val Thr Met Glu Asp Leu Ile Arg
370 375 380

ro Trp Phe Pro Glu Phe Ser Glu Ala Arg Ala Ile Met Leu Ser Arg
35 390 395 400

ly Leu Ala Phe Gly Tyr Gly Leu Leu Cys Leu Gly Met Ala Tyr Ile
405 410 415

er Ser Gln Met Gly Pro Val Leu Gln Ala Ala Ile Ser Ile Phe Gly
420 425 430

et Val Gly Gly Pro Leu Leu Gly Leu Phe Cys Leu Gly Met Phe Phe
435 440 445

ro Cys Ala Asn Pro Pro Gly Ala Val Val Gly Leu Leu Ala Gly Leu
450 455 460

al Met Ala Phe Trp Ile Gly Ile Gly Ser Ile Val Thr Ser Met Gly
55 470 475 480

ne Ser Met Pro Pro Ser Pro Ser Asn Gly Ser Ser Phe Ser Leu Pro
485 490 495

ır Asn Leu Thr Val Ala Thr Val Thr Thr Leu Met Pro Leu Thr Thr
500 505 510

ıe Ser Lys Pro Thr Gly Leu Gln Arg Phe Tyr Ser Leu Ser Tyr Leu
515 520 525

p Tyr Ser Ala His Asn Ser Thr Thr Val Ile Val Val Gly Leu Ile
530 535 540

.l Ser Leu Leu Thr Gly Arg Met Arg Gly Arg Ser Leu Asn Pro Ala
5 550 555 560

r Ile Tyr Pro Val Leu Pro Lys Leu Leu Ser Leu Leu Pro Leu Ser
565 570 575

s Gln Lys Arg Leu His Cys Arg Ser Tyr Gly Gln Asp His Leu Asp
580 585 590

r Gly Leu Phe Pro Glu Lys Pro Arg Asn Gly Val Leu Gly Asp Ser

595 600 605

rg Asp Lys Glu Ala Met Ala Leu Asp Gly Thr Ala Tyr Gln Gly Ser
610 615 620

er Ser Thr Cys Ile Leu Gln Glu Thr Ser Leu
25 630 635

!160

.0> 36
.1> 666
.2> DNA
.3> Homo sapiens

)0> 36
ıggcttgg ctgcgccctc tcgcgccgca cgctctgcgg gttcctccct tcttccgagc
60

:tcctctg gccgccgcgc gggagagagg ccgagatggc agatgagatt gccaaggctc
120

ɼtcgctcg gcctggtggc gacacgatct ttgggaagat catccgcaag gaaataccag
180

ıaaatcat ttttgaggat gaccggtgcc ttgctttcca tgacatttcc cctcaagcac
240

ıcacattt tctggtgata cccaagaaac atatatccca gatttctgtg gcagaagatg
300

ɼatgaaag tcttcttgga cacttaatga ttgttggcaa gaaatgtgct gctgatctgg
360

:tgaataa gggttatcga atggtggtga atgaaggttc agatggtgga cagtctgtct
420

:acgttca tctccatgtt cttggaggtc ggcaaatgca ttggcctcct ggttaagcac
480

ttgggga taattttctc ttctttaggc aatgattaag ttaggcaatt tccagtatgt
540

gtaacac acttattttt gcctgtgtat ggagagattc aagaaataat tttaaaaccg
600

acataat aaaagacatt gttgcatggc ttgtaaaaaa aaaaaaaaaa aaaaaaaaaa
660

aaa
666

0> 37
1> 3683
2> DNA
3> Homo sapiens

0> 37
ggcaggc ggcggctgca gggcaggtcc aggggccaca tggctgaggg ggacgcaggg
60

.200

:ttatttg ggagaactaa tttgaactta atcaccactt catctaattt tagcaaggta
.260

ıgttgccc agggcagtac ctgaattaac tgtccatttc agtacatgtc aagtgccttt
.320

:aggtgga gaagaaatgt ctctagagga atataaatac ctgatttctt gtcatcgaga
.380

:ttgtact gttaaatgaa tattgccttt tactgctctt tatggcttat tggaatagga
.440

.catttaa gattgatctt ggagagtttc ttcttgtgat tttagttcat aagtatgtca
.500

.ttcattt tatagtgttc atcattgagt aatggattaa gtgaaaatcc aggagtatcc
.560

:tgcagtt atgtgctgag gtgataattc atccaacata tttgttagca taaatattat
.620

.tcagttt ctgttgcaaa ttggtgattg tgaaattaca gaaagtgatt ttctagtctg
.680

.tttttgt ttaattcttg taatgtaagc aataaatatg gagtgtcagt agtctccttc
740

:cccagaa atgtgttggt gtaacattct cgtttctttt aacaacctgg aagtaccttt
800

gtgatct tcactgagga attagaacta tgatagaagt taggctgtgg caaatgggac
860

cgtagag tgggatagag gtggcagaat gaacctggtg tagggcagga gtatgttgtg
920

ttacatc aatttgatgc atgctttcca tctgcactcc agacggcttt ctcagttcca
980

ttttgca gagagaagga gcaaaccttt tcattggaaa aacagaaaca accctccccc
040

ttttttc ccctctattc atcaaacctt tatgtatctt tcatcttcca gttacctcta
100

atttaga tagtgaaatt tacctttgag atataacaat aagtgattaa ctgttcactt
160

gatgtaa tggcaaacaa ttgttaaaag ttattaactg atcacagatt tgcctggact
220

cttccca gggagggaac agaagttagg aggcaacttt gggatggtgc tagagcatgg
280

eolf-seql-S000001.txt
gcgaccaga ggcagaatga ggaaattgaa gcaatggcag ccatttatgg cgaggagtgg
120

gtgtcattg atgactgtgc caaaatattt tgtattagaa ttagcgacga tatagatgac
180

ccaaatgga cactttgctt gcaggtgatg ctgccgaatg aatacccagg tacagctcca
240

ctatctacc agttgaatgc tccttggctt aaagggcaag aacgtgcgga tttatcaaat
300

tccttgagg aaatatatat tcagaatatc ggtgaaagta ttctttacct gtgggtggag
360

aataagag atgttcttat acaaaaatct cagatgacag aaccaggccc agatgtaaag
420

gaaaactg aagaggaaga tgttgaatgt gaagatgatc tcattttagc atgtcagccg
480

aagttcgg ttaaagcatt ggattttgat atcagtgaaa ctcggacaga agtagaagta
540

agaattac ctccgattga tcatggcatt cctattacag accgaagaag tacttttcag
600

acacttgg ctccagtggt ttgtcccaaa caggtgaaaa tggttctttc caaattgtat
660

gaataaga aaatagctag tgccacccac aacatctatg cctacagaat atattgtgag
720

taaacaga ccttcttaca ggattgtgag gatgatgggg aaacagcagc tggtgggcgt
780

cttcatc tcatggagat tttgaatgtg aagaatgtca tggtggtagt atcacgctgg
840

cggaggga ttctgctagg accagatcgc tttaaacata tcaacaactg tgccagaaac
900

actagtgg aaaagaacta cacaaattca cctgaggagt catctaaggc tttgggaaag
960

caaaaaag taagaaaaga caagaagagg aatgaacatt aatacctgaa actataggaa
1020

gttaattt gcctataatt atatatacat tccatagtca tcaaggaata tattgtgcag
1080

gagtatc cttgactgct taagtcagcc agttcagcat ggataccaac attagctttt
1140

cttggtt atatcatctg ccaaaaatag agaacttatg atctattcat gtgtgtttca

eolf-seql-S000001.txt

ıgcacaga gaattggaca aacaggtctt tttctctttt ctctgatgtt ttacctttaa
:340

jatccaac atccttaccg ttggtatttt tagtaaggtt atagtaaata gctttacacc
:400

jatggatt ctgaaatata aattctaaat tatatttgtt ataactatat tttatgttgt
:460

jttatcag gagccatcag agaatgacct ttttgtgttt ggaacacttg gttccatgaa
:520

jtatgctt tgtgttttaa ctgttaaaat aatttaaaaa ttaattattt tacataatta
:580

jaagttaa aaactattaa cattaaataa tttcacaatt tcaacatgtc aaacctatga
:640

ıgagatag gaaacaatga gaaacttact tttgctcctt tatacagaat tattaactat
:700

.ttactaa ctaaaaaact ctagtattct ttacctaaag tcaattggct ggtaagaggg
:760

ıgatgcaa aattctccag ctctgaactt ggagctactt cacactctac tcttaatgga
:820

:ttgaact aatgatagat agtatttttt tcctctattt aaaatttttg tcttgattag
880

atttttc agttctccat ataataattt tctacaatca gatctatgct gtggcatatt
940

ctttatt taaaaatttt tttttagaga tgagttcttg ctctgtcacc taggctggag
000

agtggca tgatcatggc tcactgcagc cttgaccttc cagcctgcca agtagctggg
060

acagaca ggcatgtgct attacacctg gctaattttt aaagtttttt ttgtaaagat
120

gtctttc tatgttgccc aggctcgtct tgagctcctg gcctcaatcg atcttcctgc
180

ggttttg gaattacagg tgtgagccac catgcctggc ctgctttgac atattttata
240

tgttaat tacaaatagt cttcatatgc cagaatataa gagcaagtgt tatctacttt
300

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eolf-seql-S000001.txt

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3480

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3540

tatgcatg attttgtata tatggttatt tttctttcca taaaaatggt attaaactgt
3600

atactgtt ttgtagccta catatttcat atagaagtat attgttaaca ttttccatgt
3660

ataaatat tctatggctt tct
3683

10> 38
11> 3251
12> DNA
13> Homo sapiens

00> 38
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gcgccccc tccgcgcgcg ccctcccccg agtgcggagc gggaggaggc ggcggcggcc
180

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240

ggaggagg ccgaggcgcc ggaggaggcc gaggcgccgg agcaggagga ggccggccgg
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480

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eolf-seql-S000001.txt

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720

aaactctc caagatattg tatacaaatt agttccaggg cttttcaaaa atgaaatgaa
780

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840

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960

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1080

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1200

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1800

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1860

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1980

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2040

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2100

ccgtttat tttactgact tgtttaaatg attcgctttt gtaagaatca gatggcatta
2160

cttgttgt acaatgccat attggtatat gacataacag gaaacagtat tgtatgatat
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2280

cccaactg gttcgacctt tgcagatacc cataacctat gttgagcctt gcttaccagc
2340

agaatatt tttaatgtgg atatctaatt ctaaagtctg ttccattaga agcaattggc
2400

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2460

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:120

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·180

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·240

.aaaaaaa a
251

0> 39
1> 2855
2> DNA
3> Homo sapiens

0> 39
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60

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180

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240

caggccc cagacatgct gcatagattt tatggaaaga actcttctta tgtccatggg
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ttggatt caaatggaaa gccagcagat gcagtctacg gacagaaaga aatccacagg
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480

eolf-seql-S000001.txt

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600

jcctcagg aggagtctga agaagaagta gaggaacctg aagaaagaca gcaaacacct
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jgtggtac ctgatgattc tggaactttc tatgatcagg cagttgtcag taatgacatg
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200

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320

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1680

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2400

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2760

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2820

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2855

10> 40
11> 1396
12> DNA
13> Homo sapiens

00> 40
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720

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```
    #                                                        ##
                                                              #
  ####   ## ###   ####   ### ##### #  #   ####   ## ##    ### #
     #    ##     #    #   #   #  ## ## # #    #   ##  #  #   ##
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Job : 14
Date: 4/11/2007
Time: 11:27:02 AM